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A DISCUSSION OF ACIDOSIS.*

WITH SPECIAL REFERENCE TO THAT OCCURRING IN DISEASES OF CHILDREN.

By JOHN HOWLAND, M. D., and W. MCKIM MARRIOTT, M. D.

(From the Harriet Lane Home and the Department of Pediatrics of The Johns Hopkins University.)

The term acidosis is one that, at the present time, is very generally and very loosely employed in clinical medicine. It is used, for the most part, to indicate that acetone bodies have been found in the urine by qualitative tests. In descriptions of most of the recorded cases, however, those symptoms that we may look upon as important for the diagnosis of acidosis are not to be found. It is assumed that the acetone bodies are very abnormal and that their presence signifies an unusual complication in the course of disease. Whereas, we may, in many instances, liken the mere presence of acetonuria to fever; for it occurs in most of the infectious diseases of children with much the regularity that fever does. We do not look upon moderate fever associated with infectious processes as unusual or dangerous, nor should we look upon the acetone bodies in the urine as unusual or dangerous. Hyperpyrexia may, however, develop and in itself be dangerous or fatal. So, too, a production of the acetone bodies may in itself determine a fatal outcome.

*Read before the New York Academy of Medicine, December 2, 1915.

But the quantitative difference between the mere presence of the acetone bodies and their production in amount sufficient to threaten life is an enormous one. If we speak of a slight production of acids as acidosis, we might say that acidosis is the rule in health, for acids are always being formed in the body and means are always being taken to neutralize and get rid of them; carbon dioxide, a weak acid, is always being given off from the lungs and the kidneys are usually excreting an acid urine. The mere changing of the diet from an ordinary mixed one to one of meat, cereals, bread, butter and prunes, calls upon the defensive mechanism of the body to an extent as great as would the production of several grams of β-oxybutyric acid in the course of 24 hours. This is chiefly due to a change in the mineral constituents of the food. We would hardly be justified in saying that a person on a diet of bread, butter, rice, meat and prunes was suffering from acidosis.

Moreover, it is not the mere presence of the acetone bodies that determines acidosis. In children they are not a very frequent cause. To understand how acidosis may be brought about, or, in other words, how the normal relationship of

alkalies to acids in the body may be disturbed, it is necessary to consider briefly the method by which the body maintains its equilibrium, in which there is a preponderance of bases over acids.

With extraordinary regularity the blood is maintained at a constant reaction which is slightly alkaline. It is unnecessary to dwell upon the necessity for constancy of reaction further than to remind you of the extreme sensitiveness of the enzyme and chemical actions in the body, which are interfered with or absolutely inhibited by the most minute alterations of reaction in the various fluids. For instance, a change in the reaction of the blood from the normal one to precise neutrality is sufficient to render life impossible. That is, a change from the reaction of ordinary tap-water, which is more alkaline than the blood, to that of distilled water, which is much more acid than blood, would be incompatible with life.

The body is constantly elaborating acids as the result of oxidative processes in intermediary metabolism. For example, sulphuric and phosphoric acids result from the oxidation of the sulphur and phosphorus of proteins, and carbonic acid from the transformation of all organic material. In addition, certain organic acids are formed in small amounts and are usually transformed completely into carbon dioxide and water, although a small quantity of such substances as lactic and uric acids does leave the body unchanged. Also acid radicles predominate in the mineral constituents of many of the common foods. To guard against the deleterious influence of the acids formed in or introduced into the body, a most efficient mechanism is available. It is only necessary to consider here the mechanism from the standpoint of the blood, for this serves to regulate the reaction of the entire body.

The important constituents of the blood, so far as the regulation of the reaction is concerned, are: (a) sodium bicarbonate, occurring both in the plasma and in the cells; (b) the acid and alkaline phosphates of sodium and potassium, found almost entirely within the red blood cells, and (c) the proteins.

Considering the blood first as a solution of sodium bicarbonate: A large amount of acid, carbonic acid, is constantly being formed in the tissues. It must be removed by the lungs, but first it must be transported to the lungs by the blood. This stream of acid which, with an adult, in the course of the day, is the chemical equivalent of several hundred cubic centimeters of concentrated hydrochloric acid, is sufficient to render acid any ordinary solution and keep it permanently acid. If this should happen in the blood, life would, of course, be impossible, but owing to the laws that govern the reaction of solutions of weak acids and their salts, the solutions of sodium bicarbonate are able to take up a quantity of the acid, carbon dioxide, without appreciably undergoing a change in reaction. Thus there can be transported from the tissues to the lungs, and so continuously eliminated from the body, a very large amount of acid. This steady escape of acid is accomplished with no harm and with no strain upon the organism. The respiratory center is adjusted to assist in the removal of the carbon dioxide. If there were no respirations and the circulation were continued, eventually the carbon-dioxide concentration would be the same in the tissues, in the blood and in the air in the pulmonary alveoli. But the respirations lower the concentration in the lungs and thus allow the carbon dioxide to escape from the tissues where the concentration is highest, by the blood where the concentration is lower, to the air in the lungs where the concentration is lowest. The respiratory center is extraordinarily sensitive to the slightest alteration in the reaction of the blood toward the acid side, so that an increased production of carbon dioxide in the tissues, such as occurs for instance with muscular exercise, and the resultant slight excess in the blood are answered by an increased ventilation of the lungs, which removes the carbon dioxide, thereby bringing the reaction of the blood back to normal. Other acids, whether formed in the body or introduced from outside, produce a similar effect. They displace the carbonic acid from the sodium bicarbonate and set carbon dioxide free. This excess of carbon dioxide is removed by the increased pulmonary ventilation, leaving a neutral salt—sodium β-oxybutyrate or chloride or what not—to be removed by the kidneys. Such a mechanism allows relatively huge amounts of abnormal acids to be at once rendered innocuous and removed. For instance: $NaHCO_3 + HCl = NaCl + H_2O + CO_2$. The hydrochloric acid is neutralized and the resultant sodium chloride is removed by the kidneys, while the carbon dioxide is given off by the lungs.

Henderson[1] calls the carbonates of the blood the first line of defense. Thus, dyspnœa, more properly hyperpnœa or increased pulmonary ventilation, under abnormal circumstances, is an agent of the greatest value in ridding the body of carbon dioxide and thus keeping the reaction within normal limits. It may also be remarked that hyperpnœa is the best of all the evidences of acidosis to be obtained by physical examination alone. It may almost be said that hyperpnœa means acidosis.

If the bicarbonates of the plasma furnished the only method of defense of the body, the organism would succumb to acidosis as soon as the bicarbonate was depleted by the excretion of neutral salts through the kidneys; every molecule of an acid would rob the body of a molecule of bicarbonate. The second mechanism here comes into play and is that by which acids may be removed, leaving behind part of the base with which they have been combined, this base being available for further neutralization. The elimination is by way of the kidneys. These have the capacity to excrete an acid urine from a nearly neutral blood. They remove acid phosphate and save base with each molecule of acid phosphate that they excrete. Thus, although alkali is eliminated in the urine, it is much less than would be the case without this specialized kidney activity and can readily be replaced under normal circumstances by the alkali of the food. For instance, with the introduction of a foreign acid: $Na_2HPO_4 + HCl = NaCl + NaH_2PO_4$. The hydrochloric acid is neutralized, the sodium chloride and acid sodium phosphate are excreted by the kidneys. Or the following reaction may take place: $Na_2HPO_4 +$

[1] Henderson, L. J.: Amer. Jour. of Physiol., 1908, XXI, 427.

$H_2O+CO_2=NaH_2PO_4+NaHCO_3$. By this method, the sodium bicarbonate reserve of the body is renewed.

Henderson and Adler [3] showed the magnitude of alkali sparing very prettily by titrating with alkali the acid urine back to the normal reaction of the blood. The alkali spared was found in normal adults to vary, in terms of tenth normal alkali, between 200 and 800 cc. This is equivalent to saying that the kidneys eliminate from 200 to 800 cc. of tenth normal acid in 24 hours.

A third method of defense is afforded by the proteins. The part they play is probably not so great as that of the bicarbonates or phosphates. It depends upon their amphoteric character. Proteins can combine with appreciable amounts of either acids or alkalies without undergoing marked changes in reaction. The details of this action are obscure, but the influence of protein is undoubted. These three means of defense, bicarbonates, phosphates and protein, act synchronously and reside in the blood itself. There are undoubtedly similar measures of defense in the tissue juices and cells of the body.

The body possesses a further means of defense in that it is able to neutralize acid by the production of alkali. The alkali to which we refer is ammonia. In health a small amount of this is always formed and neutralizes an equivalent amount of acid. When acids are introduced into, or formed in, the body in unusual amount, a response occurs in an increased production of ammonia. This is formed at the expense of urea, a neutral substance, and hence represents a clear gain of alkali to the body. The amount of alkali saved to the body in normal subjects approximates that saved by the process of acid-phosphate excretion, but in abnormal conditions, such as diabetes, it may save ten times as much. With such findings it is unnecessary further to emphasize the fact that in ammonia production the body possesses a magnificent means of defense against acids.

From the foregoing, it must be plain that there may be all degrees of acid production and retention. As a result of this it is very difficult to set a limit and say when acidosis is present. There is a range of variation of the temperature in health. Does an elevation of a tenth of a degree above this constitute fever? When can we say that fever begins? It is even more difficult to say when acidosis begins, for the reason that we recognize acidosis largely by the exhibition of increased activity in those defenses that are constantly in operation. Let us, then, consider the means by which it is recognized: We may examine the urine or the blood for the presence of abnormal acids. They may be found and, when found, are evidences of an alteration in the ordinary metabolism; but their mere presence does not indicate that acidosis exists, for they may be entirely compensated for by the various means that have been enumerated, and the functions of the body may be in nowise interfered with on account of their presence. They are in themselves not essentially toxic, and they can prove harmful to the body only by removing bases. In excessive amounts they are productive of great harm in this way, but this harm can be shown by other methods. Severe and fatal acidosis may, on the other hand, occur when no abnormal acids can be found.

We seek for the evidence of unusual activity of the body's defenses. We determine the amount of ammonia excreted in the urine and its relation to the total nitrogen excretion. This is one of the oldest and most generally employed methods. In may cases of acidosis the ammonia excretion is increased both absolutely and also in relation to the total nitrogen output. A high ammonia coefficient, however, occurs as the result of certain dietetic changes. A high ammonia coefficient always arouses the suspicion of acidosis, but, unless this can be confirmed in some other way, should not be taken as conclusive proof of its presence. On the other hand, fatal acidosis may occur in uræmia and in nutritional disorders of infants with no considerable increase in the ammonia coefficient.

We determine by other means than by mere observation the evidences of increased pulmonary ventilation. This may be done by spirometer measurements, as carried out by Peabody, or by the determination of the carbon-dioxide percentage in the alveolar air. The carbon-dioxide percentage or, more correctly, tension of the blood and of the alveolar air, is the same. The tension is diminished in acidosis.

Why is there a diminished carbon-dioxide tension of the blood in acidosis? For one reason because there is less bicarbonate in the blood. Some of it has been taken to neutralize acids, and what is left is not capable of maintaining the normal reaction of the plasma, when carbon dioxide in the usual amount is poured into it from the tissues. A relative excess of the acid carbon dioxide over the alkaline bicarbonate occurs, with a resulting shifting of the reaction toward the acid side. Thus the respiratory center is stimulated, the increased pulmonary ventilation serves to remove rapidly the carbon dioxide and the carbon-dioxide level in the blood is lowered. The blood reaction tends to return to normal, but as the carbon dioxide is constantly formed, the dyspnœa becomes constant unless the sodium bicarbonate content of the plasma is renewed. The quantity of carbon dioxide excreted by the lungs is not appreciably changed, but is diluted as the result of the increased amount of air entering and leaving the lungs. For this reason the carbon-dioxide percentage or tension of the alveolar air is lower than normal.

Bicarbonate deficiency in the plasma is an indication of acidosis. This deficiency may be recognized in a variety of ways. One of the oldest is the determination of the carbon dioxide given off from the plasma when acid is added to it. This method has recently been made applicable to clinical medicine by van Slyke.[3] A diminution in the volume of carbon dioxide given off indicates a depletion of the bicarbonate content of the blood. The test introduced by Sellards [4] also indicates a deficiency in bicarbonate in the plasma. It is carried out by removing the proteins of the serum with absolute alcohol and evaporating the filtrate with a few drops of

[3] Henderson and Adler: Jour. Biol. Chem., 1909, VI, xxxviii.

[3] Van Slyke: Proc. Soc. Exp. Bio. & Med., 1915, XII, 165.

[4] Sellards: Johns Hopkins Hosp. Bull., 1914, XXV, 147.

phenolphthalein. Under normal circumstances a deep purple color results. With acidosis the color is greatly modified or may be entirely absent. Finally the bicarbonate depletion may be roughly determined by giving sodium bicarbonate as recently practiced by Sellards,[5] Henderson and Palmer.[6] With acidosis an increased amount is necessary to bring about an altered reaction of the urine. This is usually spoken of as the tolerance to alkalies. The reserve alkali may also be determined by titration of the blood with dilute acid.

We have described the methods by which the body protects itself against acids and maintains the normal reaction of the blood. The defenses may break down. When they do, the reaction of the blood changes. The reaction of the blood may be determined either by the electrical method or by the recently introduced "dialysis-indicator method."[7] What is determined is the concentration of hydrogen ions. An acid is a substance giving hydrogen ions in solution, an alkali is one giving hydroxyl ions in solution. When the amount of these is equal, the solution is neutral. If the hydrogen ions predominate, it is acid. In any solution both hydrogen and hydroxyl ions are present and their product is a constant. When one increases, the other diminishes. It is thus possible to express the reaction of any solution by stating the concentration of either hydrogen or hydroxyl ions. In uncompensated acidosis the hydrogen ion concentration of the serum is increased. Coincident with this is a diminution in the capacity of the hæmoglobin to combine with oxygen.[8]

The methods that we have ourselves used in the cases to be described have been chiefly the determination of the carbon dioxide in the alveolar air, Sellards' test, the alkali tolerance, the determination of the hydrogen-ion concentration of the serum and the oxygen-combining power of the hæmoglobin, and the quantitative determination of acetone bodies in the blood[9] and urine.

To consider first the acidosis resulting from the production of abnormal acids: In childhood they are chiefly found in diabetes and in recurrent vomiting. We will not discuss in detail the acidosis of diabetes. It was the earliest recognized, has been the most studied and is the best understood. We have nothing of importance to add to it. But a study of diabetes in children shows very well the enormous amount of acid that may be taken care of with no disturbance of the reaction of the blood and with no effect upon the respiration. Thus, three of our patients, small children, excreted daily in the urine 4.7, 5.5 and 5 gm. of β-oxybutyric acid, respectively. They had also, instead of only a few milligrams of acetone bodies per 100 gms. of blood, as is normally the case, more than 50 milligrams each, a very considerable accumulation of these substances. There was no evidence of acidosis except the presence of these abnormal acids and a high ammonia coefficient.

In recurrent or cyclic vomiting the conditions are more obscure. Why should the acetone bodies be produced in excess? It would seem that the explanation is not always the same. Alonzo Taylor[10] has found from the observation of one typical case that the acetone bodies did not appear until two or three days after the onset of the attack, and were then excreted only in moderate amount. The conditions were comparable to starvation and the presence of the acetone bodies might be referred to the starvation. Hilliger[11] observed the production of attacks of recurrent vomiting by limiting the carbohydrate intake. When the blood sugar fell to .07 per cent, an attack was precipitated. But we can hardly look upon carbohydrate restriction as the usual cause of attacks of recurrent vomiting, for the majority of attacks occur with children receiving an ample supply of cereals, bread and sugar. Nor are the acetone bodies usually slow in appearing in the urine. They are often found a few hours after the beginning of vomiting. We have determined a large amount in urine voided at seven in the morning, when the initial vomiting had been at two that same morning. Such quantities cannot be accounted for on the basis of starvation.

Recurrent vomiting is a very frequent and equally obscure condition. Why should the acetone bodies be rapidly formed in excess when carbohydrates are given in sufficient amount and when the sugar can apparently be burned? For it does not appear in the urine, nor does it increase in the blood. We have studied a mild and a fatal case. The mild case was perfectly typical and occurred in a five-year-old boy, who had repeatedly had such attacks. He vomited for three days and eliminated in 24 hours 3 gm. of β-oxybutyric acid. His blood sugar was .071 per cent, singularly close to the figures that were found in Hilliger's cases with the onset of the vomiting. There was no evidence of increased activity of his defenses against the acids.

The fatal case was observed only in the last hours of life. A child, 3½ years old, began to vomit without apparent cause and when upon a rational diet. The vomiting was continuous, nothing being retained. His condition rapidly became worse and he was brought to the hospital at the end of 48 hours in coma and with hyperpnœa. Sellards' test showed a great reduction of the bicarbonate of the blood. The hydrogen-ion concentration of the blood was increased. The tolerance for alkalies was increased so much that 9 gm. of bicarbonate of soda given intravenously failed to effect an alteration of the reaction of the urine. A quantitative test for acetone bodies in the blood showed the surprising amount of 170 mgm. per 100 gm., as much as is found in the blood of an adult in diabetic coma. Clearly the acidosis was due to the acetone bodies. The autopsy findings were practically nil.

That acetone-body acidosis may occur without apparent cause in the absence of diabetes is shown by the following case: A boy of three years was sent to the hospital for a tumor of the antrum of Highmore. It was discovered that this was in all

[5] *Idem: Loc. cit.*

[6] Henderson and Palmer: Arch. Int. Med., 1913, XII, 153.

[7] Levy, Rowntree and Marriott: Arch. Int. Med., 1915, XVI, 389.

[8] Barcroft: The Respiratory Function of the Blood, Cambridge, 1914.

[9] Marriott: Jour. Biol. Chem., 1914, XVIII, 507.

[10] Personal communication.

[11] Hilliger: Jahrb. f. Kinderh., 1914, LXXX, 1.

probability secondary to an inoperable tumor of the kidney. There was nothing unusual in his condition, until one evening it was noticed that he was breathing heavily and with a slight effort. The next day hyperpnœa was marked. He sat up in bed in much distress. His respirations could be heard at a distance. There was no cyanosis. The bicarbonate of his blood as shown by Sellards' test was much reduced. The reaction of the blood had shifted markedly in the direction of acidity. He was given 7 gm. of bicarbonate of soda intravenously. Before 2 gm. had been injected a distinct improvement in his breathing was noticed, and 20 minutes after the completion of the injection he was breathing quietly and had fallen asleep. An incomplete 24-hour specimen of urine yielded 16 gm. of β-oxybutyric acid and 4 gm. of diacetic acid. Four weeks later the boy, who had been comfortable in the meantime, began again to develop dyspnœa. This was brought to a prompt termination by another infusion of bicarbonate.

Our attention has been chiefly directed to a study of the acidosis occurring in the diarrhœal diseases of infancy. Infants with severe diarrhœa may die with no evidences whatever of acidosis. This is true of the majority. On the other hand, a number of infants with severe diarrhœa do develop evidences of acidosis; and the overwhelming majority of these die. The clinical evidence of the acidosis is hyperpnœa.

We began our studies with the suggestion afforded by the hyperpnœa and have carried them over two years. Finkelstein [12] has discussed at great length the causation of the symptoms of the picture which he has called "food intoxication." Hyperpnœa is one of the symptoms of this. He refers them all to the toxic influence of food products improperly or imperfectly elaborated. His theory is capable of indefinite discussion and argument, chiefly from the clinical side, but lacks a scintilla of definite proof.

It was noticed in 1897 by Czerny [13] that infants with diarrhœa at times exhibited dyspnœa. He called attention to the similarity of their dyspnœa to that presented by rabbits poisoned with mineral acids.

It is not always easy to detect hyperpnœa in its early stages by observation alone and consequently in a few instances we have found evidences of acidosis by tests when we could not say that hyperpnœa undoubtedly was present. But when there has been deep, labored breathing without cyanosis, we have always been able to obtain other proofs of acidosis.

We have found a low carbon-dioxide tension in the alveolar air. So far as we are aware, determinations of the alveolar air of infants have not before been made, owing to the difficulties of collecting the air. We have modified Plesch's [14] method so that it is applicable for use with infants. Whereas the carbon-dioxide tension of the air in normal infants or those without acidosis varies between 35 and 42 mm., in acidosis it is less than this, frequently between 15 and 25 mm. That this is due to acidosis is strongly indicated by the fact that bicarbonate of soda, given by mouth or intravenously, causes a return of the carbon-dioxide tension to normal or even abnormally high figures and to cessation of the dyspnœa. We have found that evaporation of the protein-free serum with phenolphthalein (Sellards' test) is positive with these infants. In beginning acidosis, the color is pink instead of purple; when acidosis is marked, there is no color.

We have found a great tolerance for alkali, so that relatively large amounts of bicarbonate of soda must be administered in order to change the reaction of the urine. We have determined directly the reaction of the blood by the indicator method, and have found in all the severe cases a distinct shifting of the reaction in the direction of acidity. This reaction may again become normal after alkalies have been given in sufficient quantity. And finally, we have obtained evidence of an alteration in the reaction of the blood, by determining a great lowering of the combining power of the hæmoglobin for oxygen.

The following case may be taken as representative of several that we have examined: An infant was breast-fed for two months and did well, gaining weight satisfactorily and having no digestive symptoms. He was then weaned and given condensed milk. At the end of one month of this feeding he suddenly became irritable and began to vomit. Four days later diarrhœa began and did not yield to treatment. He was moderately developed and nourished, but showed eviences of recent loss in weight. The skin was loose, hot and very dry. His eyes were deeply sunken and staring; his color grey but not cyanotic. His mouth was dry and his lips parched. His fontanelle was depressed. His respirations were deep, heaving, pauseless, and were accomplished with distinct effort. His heart sounds were of poor quality. His liver was enlarged. He lay usually in a semi-stupor, but when roused was very irritable and cried with a shrill, distressed cry. His white cells were 15,000. His temperature was between 99° and 101° F. His stools were large and consisted only of a brown, watery fluid. The carbon-dioxide tension of his alveolar air was 15 mm., as compared with the normal of 35 mm. The bicarbonate of his blood was much reduced. The reaction of his blood had changed toward acidity and the combining power of the hæmoglobin for oxygen was one-fourth that of the normal. The acetone bodies in his blood were not increased. Despite the administration of alkali, by mouth and subcutaneously, he died eight hours after admission to the hospital.

The evidence of acidosis is sufficient. Now what is it that produces this acidosis? Is it the production of abnormal acids such as β-oxybutyric acid? In cases with profuse diarrhœa they have not been found. Occasionally there may be a trace of acetone bodies in the urine, but not a sufficient quantity to account in any way for the symptoms. Keller [15] long ago sought them in vain. They are also not greatly increased in the blood and we have never found more than 25 mgm. per 100 cc. of blood, a smaller quantity than we have found in cases of diarrhœa uncomplicated by acidosis.

[12] Finkelstein: Jahrb. f. Kinderh., 1907, LXV, 1 *et seq.*

[13] Czerny: Jahrb. f. Kinderh., 1897, XLV, 274.

[14] Plesch: Zeitschr. f. exper. Path. u. Therap., 1909, III, 380.

[15] Keller: Malzsuppe, eine Nahrung für magendarmkranke Säuglinge, 1898.

If no abnormal acids are to be found, what other explanation can be offered? Is it due to loss of bases? Keller [16] sought for abnormal acids in an endeavor to account for the high urinary ammonia which is at times present with diarrhœa. In their absence, he had no explanation to offer. Steinitz,[17] in 1903, examined the stools in diarrhœa and found an excess of sodium passed by the bowel. A negative sodium balance was thus produced, more being passed in the stools than was ingested in the food. The more recent and much more extensive studies, made at the Babies' Hospital under Dr. Holt's direction,[18] confirm the finding of sodium in excess in diarrhœal stools. Steinitz spoke of his finding as a relative acidosis, believing that alkali was lost to the body and that ammonia was produced to take its place and to neutralize the ordinary acids, such as sulphuric and phosphoric. But in order to prove this, it is necessary to show that potential alkali has been lost or, in other words, alkali capable of neutralizing acid and not merely a neutral salt. For example, an excess of sodium chloride in the stools does not indicate an alkali loss. Uncompleted studies made in our laboratory seem to show that potential alkali is not lost in diarrhœal stools. At the present time it cannot be maintained that an excess of sodium or potassium in the stools shows acidosis.

In the absence of proof that abnormal acids are present or that base is lost, what further explanation for the production of acidosis can be offered? There is one striking symptom of the severe acidosis of diarrhœa in infancy, and that is a diminution in the output of urine. Complete anuria is by no means unusual. The kidneys are active in removing acid from the body. We have pointed out that the kidneys of the adult eliminate a large amount of acid each day. Suppose that only part of this acid can be eliminated. Some remains in the blood, constantly acting to reduce the alkalinity; for it is constantly being formed. With the knowledge now available this seems a rational explanation, and we are at present engaged in a study of this phase of the question.

Though explanation as to its origin may be entirely lacking, there is no doubt that acidosis occurs in the course of other diseases. It has been suggested by Lewis and Barcroft [19] that some of the symptoms of pneumonia may be due to acidosis. Two cases that we have observed presented evidence of this complication. A description of one will suffice. A child, two years old, was taken acutely ill with fever and later convulsions. He was admitted to the hospital semi-comatose with the typical breathing of air-hunger, deep, pauseless respirations quite unlike those ordinarily seen in pneumonia. He had consolidation of the left lower lobe. The bicarbonate of his blood was much reduced, and the reaction of his blood had shifted toward the acid side. There was no increase in the acetone bodies. He was infused with sodium bicarbonate solution, with a distinct change in the character of the breathing; but he died 54 hours after the onset of the disease. The pneumonia was caused by Friedländer's bacillus. A second case in a girl of six, also rapidly fatal, was caused by a pneumococcus of the type of *Group 1* of Cole's classification.

Even when no evidence of disease can be detected to which the acidosis can be referred, acidosis may be found. For instance, a boy of six was suddenly taken ill with high fever. Inside of 12 hours he was brought to the hospital with great dyspnœa of the air-hunger type. Physical examination was quite negative except for a purulent otitis media. All the tests made indicated acidosis. The bicarbonate of the blood was greatly reduced. The reaction of the blood had shifted markedly toward acidity and yet the acetone bodies in the blood were not greatly increased. The tolerance for alkalies was enormously increased. Though he took by mouth 20 gm. of soda and 6 gm. by rectum without vomiting or diarrhœa, no change in the reaction of the urine was produced thereby. But the alkalies had a profound influence upon his condition; his respirations diminished in rapidity and depth, the evidences of acidosis to be obtained by the various tests rapidly disappeared and he made an uninterrupted and apparently complete recovery; for he now seems entirely well and has been so for six months.

We may then say that acidosis is not an uncommon condition in infancy and childhood; that while it is especially frequent in the severe diarrhœas of infancy, it may appear with a variety of diseases, and sometimes, apparently, alone. To recognize it with older children is not very difficult. The character of the respiration is usually sufficient to arrest one's attention and one or two relatively simple laboratory tests will quickly determine the question one way or the other. With infants who are irritable, restless and crying, it is much more difficult to say whether hyperpnœa is present; and yet with them it is most important to make the diagnosis early, for the reason that acidosis is such a fatal complication of diarrhœal disease in infancy. Older children react promptly and often permanently to alkali therapy. It may be possible to stop the clinical and laboratory evidences of acidosis in infants, but the patients usually die. Why they do cannot be determined at the present time. Many normal processes have undoubtedly been inhibited, perhaps permanently, and many abnormal ones stimulated. A restoration to normal conditions seems nearly impossible. For this reason we should not wait until acidosis can be demonstrated. From the beginning we should give bicarbonate of soda to infants with severe diarrhœa in sufficient quantity to render the urine alkaline and keep it so.

We may lay it down as a general maxim that as hyperpnœa indicates acidosis, so hyperpnœa indicates alkali therapy, and this for infants or older children. The alkalies may be given by mouth, by rectum, subcutaneously or intravenously. Vomiting and diarrhœa frequently render their administration by mouth or by rectum out of the question. Then one of the other methods must be employed. Intravenous administration is the method of choice, especially when rapidity of action is desired—and with acidosis rapidity of action is always desired.

[16] Keller: *Loc. cit.*

[17] Steinitz: Jahrb. f. Kinderh., 1903, LVII, 689.

[18] Holt, Courtney and Fales: Amer. Jour. Dis. Child., 1915, IX, 213.

[19] Lewis and Barcroft: Quart. Jour. Med., 1915, VIII, 97.

The superior longitudinal sinus, as advised by Marfan, Tobler and Helmholz, is available with infants, or the external jugular or femoral veins. With older children, a vein in the arm can often be employed. If facilities for the intravenous injection of alkali are not at hand, the injection may be made subcutaneously, with care that the bicarbonate has not been transformed into the carbonate, else severe sloughing of the tissues may result. A four-per-cent solution is usually employed for intravenous use and a two-per-cent solution for subcutaneous use. The quantity to be injected depends upon the size of the child, the severity of the symptoms and the effect produced, but the amount is always large. It must be given until the urine becomes alkaline; even in infants under one year, as much as 10 gm. in 24 hours may be required.

With the cases of acetone-body acidosis with no sugar in the urine and with a low sugar content of the blood, glucose by rectum, subcutaneously or intravenously seems clearly indicated in addition to the alkali. With all forms water is urgently required, especially with infants who are desiccated as a result of the vomiting and diarrhœa.

Much remains to be learned regarding acidosis. The presence of abnormal acids explains the origin of some forms, but there are others that are in nowise understood. Are there abnormal acids whose presence has not been detected? Are normal acids formed in excess? Are bases lost? Does the kidney fail to excrete sufficient acid? These are a few of the questions at present unanswered that must be answered before our knowledge of acidosis can be considered in any way complete. Much has been learned in the last few years; with the present greatly stimulated interest in the subject, we may confidently expect that the future will provide answers to many of the questions that now seem obscure.

THE USE OF SUCTION IN THE POST-OPERATIVE TREATMENT OF BLADDER CASES.

By JOHN W. CHURCHMAN, M. D.,

Professor of Surgery, Yale University.

My interest in this subject was aroused by a case of extensive carcinoma of the bladder, which could be treated only by fulguration, through a supra-pubic wound. In this patient it was necessary, at the same operation at which the cancer of the bladder was treated, to do a supra-pubic prostatectomy. In order to rid the bladder of the urinary salts which were deposited on its wall, and to hurry the healing of the supra-pubic wound, it seemed advisable to keep up continuous bladder irrigation; and to keep the patient dry and comfortable, I attempted to carry off the irrigating fluid by means of continuous suction. The apparatus was arranged as shown in Fig. 1. The sterile water used for the irrigation reached the bladder through a permanent urethral catheter (*a*) which was connected with a reservoir (*b*) provided with a drip apparatus (*c*). Into the supra-pubic wound a large caliber tube (*d*) was introduced, not deeply enough to enter the bladder itself. This tube was fastened to the abdominal binder and connected with a rotary electric suction pump (*f*), through an air trap

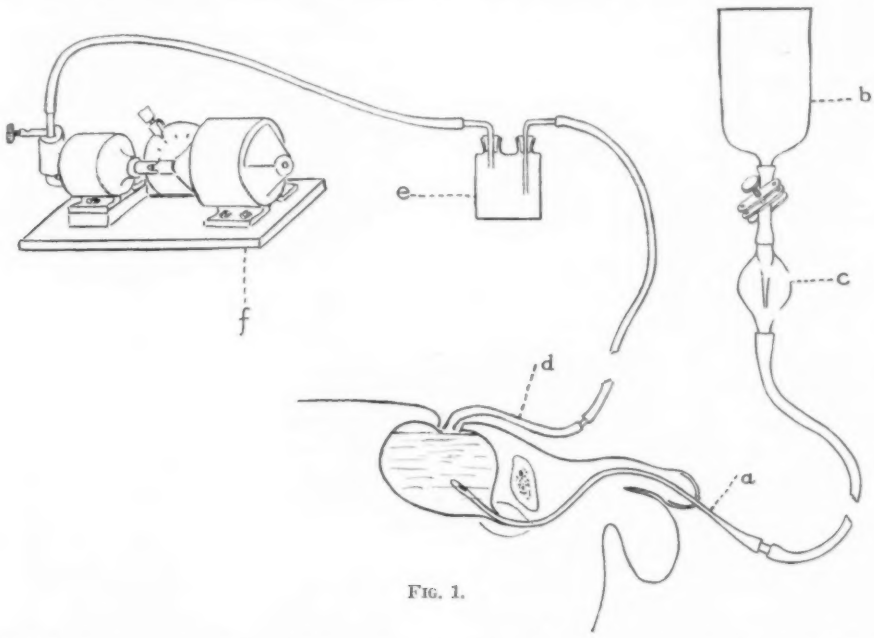

FIG. 1.

(*e*). This pump is the kind used by Dr. Flint in the post-operative treatment of empyema cases, with satisfactory results as regards rapidity of healing and cleanliness of dressings. With this apparatus it was quite easy to keep a stream of water running through the bladder and out through the operative wound; at the same time the dressings remained perfectly dry, the water being sucked away before it could reach the skin level. The results were an increase in the patient's comfort, a preservation of the skin about the wound, a saving in dressings and an increased rapidity of healing.

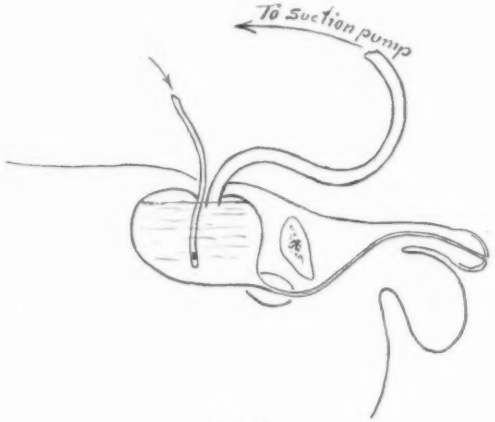

FIG. 2.

The results in this case were so gratifying that a similar arrangement was used in a second supra-pubic cystostomy, save that in this instance both inlet and outlet tubes reached the bladder via the supra-pubic wound and no permanent urethral catheter was used (see Fig. 2).

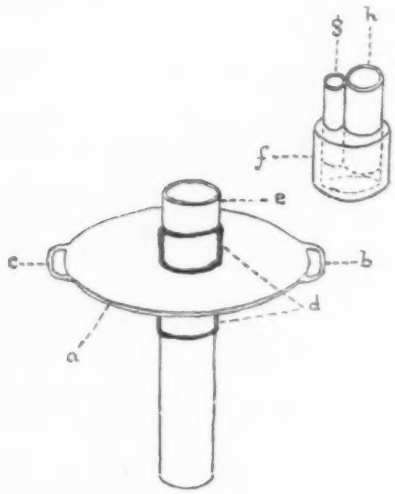

FIG. 3.

The use of combined continuous bladder irrigation and suction in the after-treatment of supra-pubic cases having been thus proved to be of value, the tube shown in Fig. 3 was devised to facilitate the application of the method. This tube consists of a metal plate (*a*) provided with two eyes (*b* and *c*) through which tapes may be passed to be tied around the waist. The center of the metal plate is pierced by a tube (*d*), through which a large caliber rubber tube (*e*)—of such diameter as to fit the metal tube (*d*) snugly—is passed. A metal cap (*f*) is made so as to fit snugly over the metal tube (*d*) in the abdominal plate. This cap is provided with two metal tubes (*g* and *h*), the smaller (*g*) for the insertion of a smaller catheter, and the larger (*h*) for a moderate-sized drainage tube. The application of this apparatus to a supra-pubic case is shown in Fig. 4. The metal plate (*a*) has been applied so that

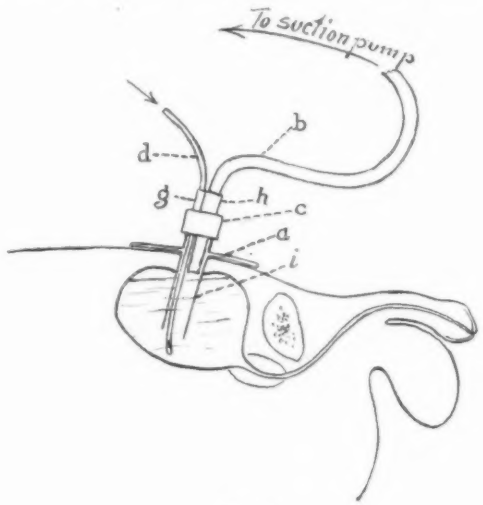

FIG. 4.

the large rubber tube (*i*) reaches well into the bladder. The cap (*c*), containing a small catheter (*d*) (which reaches to the floor of the bladder), and a large tube (*b*), has been fitted to it. Through the former (*d*) irrigating fluid is dripping into the bladder, while the excess is being drawn away, before it has had an opportunity to reach the skin level of the abdominal wound, by suction through (*b*). If either tube (*d*) or (*b*) becomes clogged, it may be removed, cleansed, and without any difficulty reinserted through the opening (*g*) or (*h*), the supra-pubic wound being held open by the metal plate (*a*), which has remained in place. If there is still difficulty with the drainage, the cap (*c*) may be removed, leaving the bladder wound still draining and kept open by the metal plate (*a*). Through this the bladder may be abundantly flushed, and afterwards the cap (*c*) with its catheter reapplied; continuous irrigation and suction are then started again.

The value of continuous irrigation, in the cystitis which accompanies hypertrophy of the prostate, has been well demonstrated by Young in his work on the perineal operation; and I have, therefore, attempted to apply it, by the method here described, to supra-pubic prostatectomy. In view of the fact, however, that the post-operative hemorrhage was not diminished, if indeed it was not increased, I have devised the ar-

rangement shown in Fig. 5 for dealing with these cases. The plate and metal tube (*a*) are inserted as usual, but the cap with its contained catheters is not applied. Through the tube the gauze packing (*b*), which is placed down to the bleeding area beneath the prostatic capsule, passes out to the abdominal dressing. At the end of 48 hours this packing is removed. The metal cap is then applied and, the hemorrhage being now controlled, irrigation and suction (as shown in Fig. 4) are instituted.

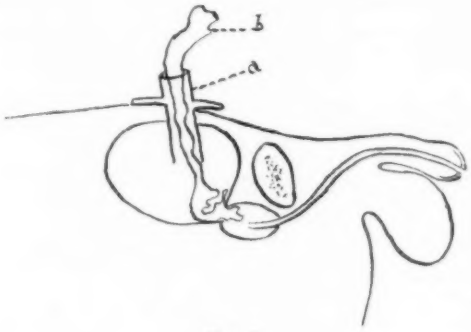

FIG. 5.

In all cases of supra-pubic cystostomy continuous suction (even when continuous irrigation is not used) is of great value in keeping the patient comfortable, saving dressing material and promoting healing; and we are now using the method with much satisfaction as a routine procedure in the New Haven Hospital. If continuous irrigation is not desired, the arrangement is as in Fig. 4, except that the catheter for the in-flow (*d*) is not used. All that is necessary to keep the accumulating urine sucked away is to have the suction tube (*b*) below the level of the skin, that is to say, through the abdominal wound. It is not necessary to have air or water-tight connections or to use strong suction. The large tube (*i*) keeps the bladder wound open and prevents suction from acting directly on the bladder wall.

The large caliber tube (*e*), Fig. 3, which fits into the metal tube piercing the plate (*d*), fits it so snugly as to prevent leakage, but it is not fastened to it and may be gradually withdrawn and shortened as healing progresses. The metal plate and tube are finally removed, and for the last days of healing a suction tube lying just in the wound, as shown in Fig. 1, is sufficient to keep the patient dry. It is to be emphasized that no air-tight or water-tight arrangement is needed; all that is necessary to keep these patients dry is a suction tube the mouth of which lies below the skin level; any fluid which reaches this level is sucked away before it has an opportunity to flow out over the abdomen.

Suction may also prove of value in other sorts of cases, where for purposes of healing it is necessary to keep the bladder empty. I have, for example, recently made this use of the method in a case of bad vesico-vaginal fistula operated on by the supra-pubic route.

With a little ingenuity the principle of continuous irrigation or suction, or a combination of the two, as here described, may be adapted to the particular needs of various sorts of operative bladder cases, and will be found of considerable value. The suction pumps needed are not expensive and one pump may be sufficient for the use of several patients simultaneously. On account of the value of suction in this class of cases, and in thoracic cases, it is planned to provide the newer wards of the New Haven Hospital with a central suction plant. Such a central plant has already been installed in one of the present wards for use in bladder cases, and in empyema cases; and plans are being made to apply a similar system of continuous suction to abdominal cases.

THE RELATION OF ANGIOGENESIS TO OSSIFICATION.

BASED UPON THE STUDY OF FIVE CASES OF CALCIFICATION AND OSSIFICATION OF THE OVARY.

By ELI MOSCHCOWITZ, A. B., M. D.,

Pathologist to the Beth Israel Hospital, New York City.

(*From the Pathological Laboratory of Beth Israel Hospital.*)

The incidence within a short time of five cases of such a rare lesion as calcification and ossification of the ovary, seemed at first a fit opportunity to study the lesion from a morphological viewpoint. A closer study of the specimens, however, revealed so many apparently novel data relating to the finer formation of bone, that inevitably the morphological becomes subsidiary to the histogenetic interest.

CASE REPORTS.

CASE 1. (B. I. H. 2891.)—Ovary removed for "chronic ovaritis." Situated beneath the capsule of the ovary is a corpus luteum that is entering the terminal phase of its evolution. It is still possible to differentiate the outer or lutein cell zone from the central core of fibrin, although both have undergone nearly complete hyaline degeneration. The outer zone contains a small number of degenerated lutein cells and radiating strands of connective tissue arising from the stroma of the ovary. The fibrinous core is acellular.

Scattered in the outer zone are a large number of focal deposits of lime (Fig. 1). These deposits are small, discrete, roughly spherical and imbedded in a cavity formed by the surrounding hyaline tissue. The core of hyalinized fibrin is free from such deposits.

The remainder of the ovary shows the changes common in the adult ovary.

Summary.—An almost healed corpus luteum within an otherwise normal adult ovary; in the outer or lutein-celled zone are scattered discrete deposits of lime.

Case 2. (B. I. H. 3529.)—S. F., aged 60, was admitted to the hospital October 19, 1912, suffering from chronic nephritis. The patient had been married 30 years, and had had six pregnancies, of which two had ended in abortions. She began to menstruate at 18 years; menopause at 40.

The main symptoms on admission were vertigo, headache, fever and sweating, marked edema of the legs, increasing weakness, cough and expectoration and loss of weight. The urine showed much albumin and many casts. Blood pressure, 200. The patient died in uremia, Nov. 7, 1912.

Autopsy.—Anatomical diagnosis: healed tuberculosis of the lungs; emphysema and congestion of both bases; brown atrophy of the heart muscle with hypertrophy of the left ventricle; chronic congestion of the liver and spleen; chronic interstitial nephritis; "osteoma" of the ovary.

Both ovaries are small and shrunken. In the right ovary, just beneath the capsule, is a mass of ivory hardness, measuring 5 x 3 x 2 mm. The mass is egg-shaped; its surface is convoluted and densely adherent to the surrounding tissue. The mass is surrounded by a narrow zone of dense white tissue resembling in structure and conformation a corpus albicans.

Microscopical Examination.—(Fig. 2). The mass consists of a homogeneous mass of lime embedded within a corpus albicans. The edge is wavy, and sharply circumscribed from the surrounding thin capsule of hyaline connective tissue. With the high power the fine fibrillar structure of the hyaline matrix can be distinguished in the calcareous area. Within the calcareous mass are clefts which are manifestly artefacts, due in all probability to the method of preparation.

Summary.—A homogeneous nodule of lime deposited in a corpus albicans of an atrophic ovary. The lime mass contains no bone or cellular elements whatever.

Case 3. (B. I. H. 2887.)—R. H., aged 40, married 12 years, no children. Menstruation began at 14, regular every four weeks, and of eight days' duration. For the past few months she has been complaining of severe pain in the lower left abdomen. Pre-operative diagnosis: fibromyomata. Operation by Dr. L. J. Ladinski. Supravaginal pan-hysterectomy.

Gross Description.—Uterus: large fibroid in fundus. Fallopian tubes; both tubes adherent to each other by dense adhesions subtending the posterior aspect of the uterus. The left tube is greatly thickened, straight and spindle-shaped. The lumen is completely obliterated and filled with a fine, white, honeycombed mucosa, which exudes a small quantity of seropurulent fluid. The muscular coat is thickened. At its thickest point, the middle of the tube, it has a thickness of 1.5 cm. The right Fallopian tube is distorted and varies in thickness. At the isthmical junction is a nodule, the size of a bean, typical of so-called "salpingitis nodosa." From this point the tube suddenly becomes narrow for a distance of 3 cm., averaging in diameter a goose-quill, whence it gradually increases in size until at the fimbriated end it is 2 cm. in diameter. The fimbriated end is closed. Section of the tube through the isthmical nodule reveals the typical microscopic appearance of "salpingitis nodosa." In the narrow portion the lumen is very small; there are no villi, and the muscular coats are slightly thickened; at the outer end, the lumen is fairly large, convoluted, and lined with a smooth glistening white membrane. Midway between the lumen and the peritoneal coat, is a thin layer of bone which is continuous around the circumference. This layer is about 2 mm. thick, and its contour conforms to the wavy outline of the tube lumen. The left ovary is greatly enlarged, edematous, and contains numerous fresh and old corpora lutea.

The right ovary is very small, measuring 2.5 x 1.5 x 1 cm., and is deeply scarred. On section a hard dense calcareous mass, 8 x 5 x 4 mm., is found just beneath the capsule. This nodule is situated within the center of a corpus albicans, being surrounded by a narrow wavy capsule of dense white hyaline tissue. The mass was shelled out with difficulty and was found to be egg-shaped, convoluted like a brain, with shallow sulci. The remaining portion of the ovary shows dense cirrhosis and a large number of corpora albicantia.

Microscopical Examination.—The masses in the uterus reveal a typical fibromyoma with hyaline degeneration.

The description of the microscopic structure of the tube is irrelevant for our purpose and will be reserved for later publication.

Calcareous Mass in the Right Ovary.—The lime is deposited within a corpus albicans, the fine fibrillar structure of which can be seen with the high power shimmering through the lime-containing area. The circumference is very wavy and finely spiculated (Fig. 3). Here and there, manifestly corresponding to the sulci observed grossly, are many bay-like excavations penetrating for short distances into the concretion. These excavations are irregular in shape, vary in size, and with the low power of the microscope appear empty. The surrounding hyaline fibrous tissue, which along the greatest part of the circumference is in close apposition to the lime-containing area, becomes attenuated over these excavations and is gradually lost at the roof of the excavation (Fig. 4). With the high power, however, these excavations contain distinct tissues. *In all these excavations without exception, we find abundant red blood cells, a fine fibrillar network of connective tissue and a few distinct fibroblasts. In some excavations, we can even distinguish a very young blood capillary, formed apparently by a number of fibroblasts arranged circularly. These capillaries contain red blood cells* (Fig. 5). The interior of the calcareous nodule also contains numerous irregular cavities with sharply defined walls, which in general features and size resemble the excavations described above. Indeed a continuity between these cavities and the surface excavations can in many instances be clearly demonstrated. Whether all these cavities communicate with corresponding excavations it is impossible to say, because the study of serial sections was not feasible. As we shall see, the probability that they do is strong. With the low objective, these cavities also appear to be empty. *With the high power, however, the same structures visible within the excavations described above are found here; namely, red blood cells, a fine fibrillar connective tissue, interspersed with fibroblasts, and occasionally very fine capillaries containing red blood cells.*

The remainder of the ovary shows the familiar changes of the hard, cirrhotic, inactive ovary.

Summary.—A patient, aged 40, with fibroids, adherent tubes and cirrhotic ovaries. The right ovary contains a calcareous concretion, the surface of which is deeply excavated, the interior honeycombed with cavities, many of which are demonstrably continuous with the excavations, all of them probably so. These excavations and cavities are occupied by an active tissue, consisting of very young blood vessels, fibrillar connective tissue and fibroblasts, in the meshes of which are many red blood cells.

Epicritical Remarks.—The source of this active tissue cannot be positively demonstrated without serial sections which, because of the unexpected findings, were not made. That this tissue arose from the peripheral blood supply cannot be gainsaid. The sequence of events is probably this: blood sinuses and attendant young fibrous tissue penetrated through the hyaline covering of the concretion from the periphery. In corroboration of this surmise, we find, in the hyaline fibrous capsule, spaces containing the identical tissues described within the excavations and the cavities. When this highly active

tissue making up a blood sinus meets the calcareous concretion, absorption of the lime occurs, resulting in deep excavations into the interior. Coincidently, the formation of young blood vessels takes place, so that part of the blood is carried within these channels.

We regard these findings and this interpretation as highly significant for the elucidation of the later processes of bone formation in these calcareous concretions, about to be described.

CASE 4. (B. I. H. 2781.)—Rosie I., aged 33, married 9 years; never pregnant. Menstruation began at 14 years; it has been regular, occurring every four weeks and of three days' duration; the flow has been normal. For the past three years she has been complaining of pain in the lower abdomen. Since then menstruation has been irregular and more frequent. It now lasts one week. On examination, there is tenderness in the left fornix. Operation by Dr. L. J. Ladinski; double salpingo-oöphorectomy.

Microscopic Description.—Both tubes are covered with remains of old adhesions. The tubes are short, straight and average 1 cm. in thickness. On section, the lumina are large; the mucosa is pale and honeycombed. The coats are thickened. The right ovary is attached by a broad pedicle to the posterior surface of the tube. It is 2.5 cm. long, 2 cm. thick and 1.5 cm. wide. *Microscopic diagnosis of Fallopian tube:* chronic salpingitis. The surface of the ovary is covered with the remains of old adhesions. On palpation a hard mass of bony consistence is demonstrable within the ovary. On removal of the mass, which is effected with difficulty owing to its intimate adherence to surrounding tissues, only a shell of ovary, about 2 mm. thick, remains. The calcareous mass is roughly ovoid and measures 1.7 x 1.3 x 1.1 cm. The surface has a brain-like contour with shallow linear sulci.

Section through the center of this mass shows that it is composed of a shell around a central cavity. The shell is 1.1 cm. thick and of bony texture and consistence. The central cavity is about the size of a pea, has a smooth wall and is filled with a soft fatty-like material resembling sebaceous matter.

Microscopical Examination of the Bony Mass Within the Ovary.—With a very low power, three fairly well defined zones can be made out: (1) an outer zone consisting of lime-containing connective tissue; (2) an inner zone of pure bone surrounding the central cavity; and (3) between 1 and 2 a narrow zone, in which new osseous tissue is in the process of formation. Each will be described in order.

Outer zone. This is rather broad, covering about two-thirds the diameter of the shell and has the same morphology as in Case 3. In other words, it consists of lime imbedded in a matrix of hyaline connective tissue. The edge is wavy, finely spiculated and sharply defined from the encircling coat of hyaline connective tissue. *Especially prominent are the same excavations on the surface as were encountered in Case 3 (Fig. 6). The difference is that they are deeper; the fibroblasts are more abundant; the reticular connective tissue is coarser; and, what is especially conspicuous, the blood vessel has a more mature appearance. The vessel is sharply defined, the coat is firmer, and cells of an endothelial type line the lumen. The red blood cells no longer lie enmeshed in the fibrillar connective tissue, but are all contained within the newly formed blood vessel. The interior of this zone also contains cavities, which, as in Case 3, correspond precisely in morphology to the superficial excavations. Here, also, communications between the two can be demonstrated.* The same description of the excavations just set forth can, therefore, be applied to these cavities. *Inner zone.* This possesses all the histological features of mature bone (Fig. 7). There are bone lamellæ, bone cells, typical Haversian canals lined with a well defined row of osteoblasts. The Haversian canals contain one, sometimes two blood vessels, fibroblasts and a fine fibrillar connective tissue. The bone trabeculæ present irregular streaky areas, which take the stain of calcification and which may be interpreted as irregular and incomplete areas of lime absorption.

The most significant observation is the exact morphological similarity, except as regards the obsteoblasts, to the excavations and cavities in the outer zone. The blood vessels, the fibroblasts and the fibrillar connective tissue correspond in every detail. The presence of the osteoblasts will now be explained. *The middle zone.* This is rather narrow, but contains within itself all the various stages of new bone formation. The earliest stage is best represented in Figs. 8 and 9. Here we note the same excavations and cavities seen in the outer zone. In addition, however, we note that the periphery of the cavity, instead of being comparatively smooth, has a broken-up, moth-eaten appearance. This change is due to two factors: (1) small, irregular scalloped-like absorptions of lime; (2) a tendency for the fibroblasts to arrange themselves along the periphery of the excavation or cavity in the form of one or more layers of obsteoblasts. *Distinct transformations of fibroblasts into the round or ovoid cells of the ostcoblastic type can be demonstrated.* Another change consists of a process of lime absorption in the trabeculæ between the cavities and an abundant deposition of cells within these trabeculæ. The trabeculæ are more translucent. The stain of the underlying hyaline matrix is more prominent. The cells are round or oval with small nuclei and stain rather faintly. *It is quite evident, however, that these cells are of the same type as those that lie on the periphery of the cavities and may, therefore, be regarded as having the same origin.*

The next step in the process of bone formation is represented in Fig. 10. Here we find the earliest form of Haversian canal. The cavities are like those already described; they contain a well-formed blood vessel, reticular connective tissue, many fibroblasts, and in addition, along the periphery, typical osteoblasts. The walls of these canals are composed partly of the calcareous hyaline matrix interspersed with cells of the osteoblastic type similar to those shown in Fig. 9; and party of typical bone foci, consisting of lamellæ and bone cells. The bone is sometimes continuous along the greater part of the periphery of the canal; sometimes it is present for short distances in two, three, or more areas of the canal with a calcareous matrix intervening. These bony zones are, as a rule, narrow, sometimes consisting of only two or three lamellæ and, peripherally, sharply defined from the surrounding calcareous matrix. This is especially true of the cavities in the more superficial parts of the middle zone. In the deeper portions the lamellæ are continuous with the osseous tissue of the inner zone.

Fig. 11 represents the last or final stage of ossification and the formation of a fully developed Haversian canal. This stage differs from the preceding only in the fact the canal is lined along its entire circumference with osseous tissue.

In the lower part of the picture we note a small Haversian canal surrounded almost entirely by osseous lamellæ.

It is highly significant for the correct interpretation of the pathogenesis of the new osseous formation, that bone is nowhere found except in immediate relation to cavities or canals. The spaces between the canals are entirely free from bone.

The tissue filling the central cavity contains merely debris and fat.

Summary.—A patient aged 33. Both Fallopian tubes and one ovary were removed for chronic salpingitis with pelvis adhesions. A bony mass is found within the ovary in the center of a corpus albicans. On microscopic section five distinct zones can be demonstrated: (1) a hyaline connective-tissue capsule derived from a corpus albicans; (2) a calcareous zone, in which are bay-like indentations and cavities each containing a blood vessel and active fibrous young tissue; (3) an

ossifying zone, in which the processes of lime absorption, the formation of osteoblasts and osseous lamellæ, and the conversion of the above-mentioned cavities into mature Haversian canals, are manifest; (4) an osseous zone consisting of mature bone, with Haversian canals; (5) a central or so-called marrow cavity showing a smooth wall, containing mostly fat.

Our epicritical remarks will be reserved until after the description of the following case:

Case 5. (B. I. H. 2883.)—I am indebted to Dr. W. C. Clarke, of Columbia University, for this specimen.

The only facts obtainable are that the mass was about the size of a walnut and was found within an ovary removed from a patient at the General Memorial Hospital, New York City.

Microscopic Examination.—The histology is the counterpart of that in Case 4, the only difference being that the process is more advanced. The three zones, calcareous, ossifying, and osseous, are distinct. The osseous lamellæ are more compact; the blood vessels both in the Haversian canals and in the cortical indentations are sharply circumscribed, possess a firm fibrous wall and are lined with "endothelium." The tissue within the forming and mature Haversian canals presents all the characteristics of fatty marrow; there is abundant fatty connective tissue, firm fibrous tissue and abundant fibroblasts, small round cells and spindle-shaped connective-tissue cells. The majority of the Haversian canals are lined with a distinct row of osteoblasts. Neither in this specimen nor in the preceding are we able to find any osteoclasts.

Summary.—With the exception of the clinical findings, the summary of this case is the same as for the preceding, the only difference being that the ossifying process has manifestly attained a more mature age.

Epicritical Remarks Concerning the Pathogenesis of Ossification in the Ovary.—We deem it a fortunate circumstance that we not only possess five cases of a lesion that is unusually rare, but that each illustrates a stage in the evolution of a process, the details of which have so far been a matter largely of speculation. It can be truly said that there are no gaps in the story that these stages illustrate. By them we are enabled to correctly interpret not only the histogenesis of so-called "osteomata" of the ovary, but also of the majority of abnormal ossifications occurring within the human frame.

Briefly, the process is the following. In the apparently dying or inert tissue of the corpus albicans, there occurs a discrete deposit of lime. This is illustrated in Case 1 (Fig. 1). By coalescence these discrete deposits form a solid amorphous calcareous mass within the center of the corpus albicans, the surface of which corresponds in a rough way to the shape of these structures. This is illustrated in Case 2 (Fig. 2). The deposition of the lime does not occur homogeneously, but within the hyaline connective tissue of the matrix of the corpus albicans as a base. In other words, should the lime be dissolved, a cavity within the corpus albicans is not formed thereby, but the underlying hyaline connective-tissue matrix will persist.

Owing to a stimulus, the nature of which is not determinable, ovarian blood vessels arising from the capsule of the corpus luteum penetrate the hyaline connective-tissue membrane and, as they approach the calcareous nodule, are transformed into blood sinuses consisting of a reticulum of delicate connective tissue and young fibroblasts, both derived from the attendant connective-tissue coat of the penetrating blood vessel. These sinuses erode the surface of the calcareous nodule and, penetrating the interior, form an inter-communicating system of cavities or canals. Some of the fibroblasts arrange themselves circularly and form a very young blood vessel, which eventually carries much of the blood that has hitherto permeated the surrounding loose fibrillar connective tissue. The canals thus formed represent the earliest stages of the Haversian canals. All these steps are nicely illustrated in Case 3 (Fig. 1). The fibroblasts now assume the function of osteoblasts. From irregular delicately appearing cells with a large faintly staining nucleus, they become larger, oval or round, with a strongly defined nucleus, richer in chromatin. These cells tend to arrange themselves along the periphery of the canals and even penetrate into the surrounding areas, in which there has coincidently occurred an absorption of lime. At the same time, the blood vessel of the canal has matured and now consists of a well circumscribed wall of fibroblasts and fibrous connective tissue. The blood vessel now contains all the circulating blood cells, none being demonstrable in the surrounding connective-tissue meshes. The surrounding reticular connective tissue is hardier in appearance, the strands being thicker, denser and interspersed with spindle cells derived from fibroblasts (Figs. 6, 7, 8 and 9).

A deposition of bone now occurs along the wall of these canals; the underlying hyaline calcareous matrix becoming converted into osseous lamellæ, the osteoblasts becoming converted into bone cells. The ossification begins at one or more areas of the wall, until finally the entire canal becomes surrounded by osseous lamellæ (Figs. 10 and 11). The ossification proceeds eccentrically, beginning in the central portions of the calcareous mass and extending peripherally. The bone lamellæ are also deposited eccentrically in relation to the individual cavities themselves, the layers becoming more numerous until they meet the lamellæ of the neighboring canal. Coincidently with this process of ossification, the contents of the canals mature progressively. The blood vessel enlarges, the fibrous tissue wall is thicker and denser and a distinct endothelial lining is visible. The surrounding reticular connective tissue is also firmer, denser, abundantly interspersed with spindle cells, and has in part become occupied by fatty connective tissue. A distinct layer of osteoblasts now lines these canals. In other words we now find an intercommunicating system of Haversian canals surrounded by osseous tissue, the whole conforming in every detail to normal calcareous adult bone.

The process is entirely analogous to the physiological endochondral ossification, the difference being that, instead of cartilage, the matrix is hyaline connective tissue infiltrated with lime. A description of endochondral ossification taken from Stöhr will show how striking this analogy is. "The first indications of this process consist in changes at certain places within the cartilage; a deposition of lime salts takes place within the matrix, in consequence of which it becomes finely granular and dull; it calcifies. Such places can soon be recog-

nized by the unaided eye, and are called centers of ossification, better perhaps, centers of calcification. Meanwhile, on the surface of the center of calcification, a tissue rich in blood vessels and young cells, the osteoblastic tissue, has made its appearance. This penetrates into the cartilage, and causes the destruction of the calcified matrix; the cartilage cells are set free and disintegrate. In this way a little excavation arises in the center of calcification; it is called the primary marrow cavity.

"These processes are repeated in the immediately surrounding cartilage; that is, the cartilage ground-substance calcifies, the cartilage cells enlarge, new portions of the cartilage break down, and as a result the primary marrow space is gradually and continuously enlarged. At the same time the capsules of many cartilage cells are opened, the cells degenerate, and the intervening calcified matrix projects into the marrow space in the form of irregular processes. The marrow cavity is now a bay-like space, filled with blood vessels and primary bone-marrow, that is, with anastomosing branched connective-tissue cells. Some of these cells, the osteoblasts, grow rich in protoplasm and apply themselves in the manner of a one-layer epithelium to the walls of the marrow cavity and there produce bone. Some of the branched connective-tissue cells retain their form and later, together with a fine-fibered connective tissue, contribute the supporting framework of the bone-marrow. Others of these cells become fat cells. Through the activity of the osteoblasts the marrow cavity is soon clothed with a thin stratum of bone, gradually increasing in thickness; the irregular processes of calcified substance are completely enveloped in young bone. Thus, step by step, the former solid piece of cartilage is transformed into spongy bone, the trabeculæ of which still contain residues of cartilage matrix."

The analogy between the pathogenesis of abnormal ossification and endochondral ossification is admitted by many observers. (Wells,[1] Buerger and Oppenheimer,[2] Mönckberg,[3] Ruh,[4] Kaufmann,[5] and Aschoff.[6]) All are agreed that the matrix for subsequent ossification is a calcified area.

Relation between Calcification and Ossification.—Calcification is a common pathological phenomenon and has been described as occurring in almost every tissue of the body. In the instances in which the process has been carefully studied, it has been found that it only occurs in areas of tissue that are dead or inert. For instance, we have observed it in tubercles, atheromatous plaques upon the lining of the circulatory system, a necrosed epithelioma of the abdominal wall, the walls of degenerated sebaceous cysts, and in the wall of an old lung abscess. On the other hand, calcification possesses a peculiar predilection for connective-tissue structures that have undergone hyaline degeneration, which, owing to their complete lack of blood vessels, can justly be regarded as inert tissues; our corpora albicantia may be cited as examples. In addition, we have observed instances of calcification in the hyaline wall of a chronically inflamed Fallopian tube, in the wall of a hernial sac of long standing, in old pleuritic thickenings, in the walls of old hydatid cysts, in old fibroids of the uterus, in the wall of a degenerated ovarian cyst and in the scar of a laparotomy wound. Indeed, this phenomenon has been observed in almost every instance when hyaline degeneration of a connective-tissue structure may occur.

The chemical process whereby lime is deposited in tissue affords an interesting and fruitful study, but is not germane to our present purpose. For an able discussion of the modern aspects of this theme, the reader is referred to the paper by Wells.

Thus far, every instance of abnormal ossification, exclusive of that directly associated with bony structures, *e. g.*, exostoses, has revealed a coexisting calcification. In no instance, furthermore, has the writer been able to discover a case of unalloyed ossification. Inasmuch as all observers agree that calcification always precedes ossification, both normal and abnormal, the postulate may be formulated that *without calcification there is no ossification.* From this postulate, we may conclude that ossification may occur in any situation where calcification has been observed. A study of recorded cases proves that this deduction is correct, so that a typographical list of abnormal ossifications becomes merely a duplicate of that of abnormal calcifications. We are not in the position to state (because in the present state of our knowledge it is obviously impossible to determine precisely) that the process of calcification ceases when that of ossification begins. In all probability, however, deposition of lime occurred on the periphery of our mass, coincidently with the ossification arising within the center. We deduce this surmise, because we have never observed, or seen reported, a case of pathological ossification within the soft tissues (independent of the bony framework) without a coexisting area of calcification.

The Relation of the Development of New Blood Vessels to the Process of Ossification.

The succession of events comprising the process of ossification, as we conceive it, agrees in its broader features with the conventional view. Our own contribution to the subject is an attempt to resolve the process to its ultimate cellular beginnings; to show how the development of new blood vessels is the essential activity in the making of bone. This activity applies not only to the making of abnormal bone, but also (and this is of vaster consequence) to the making of normal bone. To be sure, in the conventional view concerning the development of bone the important rôle that blood vessels play is well recognized. Their mere presence is accepted as an axiom, their main function being to erode the calcified ground substance so as to form Haversian canals. As we have shown, however, it is not the presence, but the development of these vessels that supplies the keynote of the process of ossification; furthermore, we have shown that the cellular elements that enter into the process of this development are the progenitors of all the histological components of osseous tissue.

The validity of this contention obviously depends upon the soundness of our exposition of the development of blood vessels. We confess that, at the outset, we felt considerable hesitancy in accepting the interpretation of the histological findings in our specimens, inasmuch as they were entirely inconsistent with

the view that we had previously been taught. Never having hitherto made an intensive study of the developments of blood vessels, we were unaware, for a time, that a conception similar to our own had already been published. By a strange coincidence, we were soon put into a close and personal touch with such studies. The result has been that whatever hesitancy we felt at first has disappeared, and we have come to the definite conclusion that the conception, independently worked out by us, is the correct one. This inevitably leads to a discussion of angiogenesis, a subject that has been the source of much controversy.

Theories Concerning Angiogenesis.—The older view * was first advocated by His and until recently was accepted by most histologists.

In this conception, blood vessels originate as protoplasmic cords arising from the terminal portion of a previously existing blood vessel. These protoplasmic cords were termed by Brenner *angioblasts,* and consisted of cellular processes derived from the endothelium of the blood vessel. By the simple process of canalization, these angioblasts become capillaries, the potential element of all blood vessels.

This conception necessarily deduces a postulate of tremendous import to cellular ontogeny, the specificity of endothelium. This has been forcibly summarized by Rabl in his dictum "Endothel stammt aus Endothel." The importance of proving whether the endothelial cell is, or is not, specific is obvious. If endothelium is specific, its functional range, both normal and pathological, at one stroke becomes a very limited one. As Schulte[7] admirably expresses it: "The doctrine of the specificity of endothelium takes endothelium out of the series of mesenchymal derivatives and separates it absolutely from the blood, should that prove to be of mesodermal origin. Consequently thinkers who support this view have seen the importance of assigning an entodermal origin to both blood and endothelium. Could this be established, it would lend a degree of antecedent probability to the doctrine of the angioblasts, but strictly speaking, it is not a necessary postulate, for a tissue arising diffusely from the mesenchyme, as development proceeds, may be confined to definite localities or even ultimately be restricted to homoplastic proliferation. Such a tissue would be specific if it yielded no heterogeneous products, and I feel myself that this latter property enters more largely into an idea of specificity as applied to tissues than the continuity or origin of their elements. It would seem, therefore, that the advocates of specificity have charged themselves rather to prove that endothelium, once formed, produces only endothelium and never any other elements, for example, blood and connective tissue, than that it is peculiar in its origin."

The modern theory of angiogenesis, first proposed by Rückert and Mollier,[8] since then warmly advocated by Huntington,[9] Schulte, McWhorter and Whipple,[10] McWhorter and Miller,[11] and Hahn,[12] assumes that blood vessels consist of clefts or spaces within the mesenchyme bounded by the indifferent mesenchyme cells. The clefts or spaces enlarge and fuse together to form blood vessels, while the lining mesenchyme cells flatten and form "endothelium." This theory has been termed the "adaptive" theory as apposed to the "specific," and predicates the postulate that the endothelial cell is a derivative from the widely distributed mesenchyme cell. To quote Schulte again: "This view thus extends the period of development, and enlarges the area in which it is active to practically the whole body of the embryo. It does not deny that endothelial cells undergo mitosis, that vessels after formation lengthen, or that they may branch and send out sprouts, for it by no means implies that endothelium does not grow, but it relegates the phenomena dependent upon endothelial cells to a later period in the life of the embryo."

This is not the place, nor indeed are we in the position, to adjudicate the arguments of the contending exponents. We have contented ourselves with merely stating the opposing views and indicating their possibilities. The data relating to this subject are immense and have been admirably criticized by Schulte, to whose monograph the reader is referred. As Schulte shows, the divergence in viewpoint is due rather to methods of interpretation than to differences in method and technique. Certainly the observations and arguments of the advocates of the adaptive theory are more convincing than those of their opponents. The recent work of McWhorter and Miller,[11] and of Hahn,[12] who showed by delicate operations upon the embryo that blood vessels formed in the area pellucida even when the angioblastic anlage in the area opaca was cut off, affords to our mind irrefutable evidence that the adaptive theory is the correct one.

However, whatever may be said as to the merits of the contending views, the fact that we independently deduced the mesenchymal origin of blood vessels from the histological study of our specimens of calcification and ossification of the ovaries leaves us no choice in the position we shall take. It may seem hazardous to transfer a conception of the development of blood vessels from the domain of the normal to the pathological, but the work of W. C. Clarke,[13] who showed that the adaptive theory of angiogenesis applies as well to the development of blood vessels in granulative tissue, eradicates whatever misgivings we may have had on this score.

The important rôle that blood vessels play in the process of ossification consists essentially in bringing into heteroplastic activity a dead or inert tissue. In the instances which we report, the tissue is hyaline connective tissue impregnated with lime salts. How is this activity brought about?

Curiously, the most obvious function of blood vessels, namely, the carrying of nutriment, is only subsidiary in the process of ossification. The main function lies in the production of new connective tissue engendered in the process of development of the blood vessels themselves. As we have demonstrated in Fig. 5, this tissue consists of two elements: (1) young fibroblasts; (2) a fine fibrillar intercellular substance. This is obviously a derivative of the fibroblasts, and its origin, therefore, need concern us no longer. The origin of the

* For the best summary of this view see Minot, Kraus and Sabin, in Keibel and Mall's "Handbuch der Entwicklungsgeschichte der Menschen," Leipzig, 1912.

FIG. 1 (CASE 1).—Healing corpus luteum of the ovary showing discrete deposits of lime in the yellow zone.

FIG. 2 (CASE 2).—Calcareous concretion within the center of a corpus albicans of the ovary.

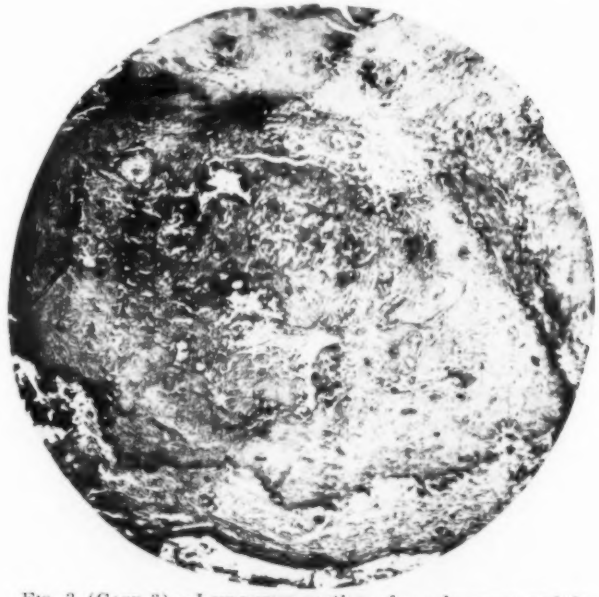

FIG. 3 (CASE 3).—Low-power section of a calcareous nodule within a corpus albicans of the ovary. Below is the hyaline connective-tissue capsule. Next to this the spiculated edge of the calcareous nodule. Within, the connective-tissue stroma infiltrated with lime, and containing spaces filled with fibrillar connective tissue, fibroblasts and red cells.

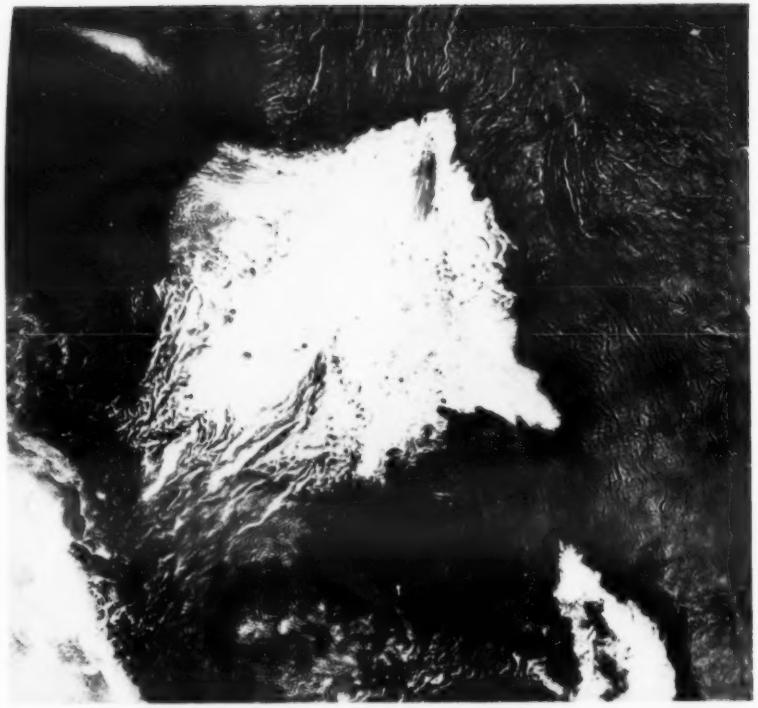

FIG. 4 (CASE 3).—Primitive Haversian canals (low power). Excavations and cavities within the calcareous nodule. These contain a fine fibrillar connective tissue, a few fibroblasts, and many red cells. These structures are very faint (staining poorly, owing to the decalcifying solution), and therefore do not photograph well.

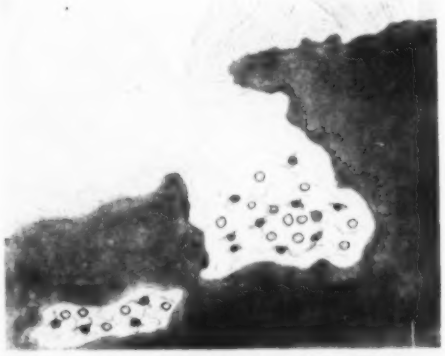

FIG. 5.—High-power sketch of the preceding (Fig. 4).

FIG. 11 (CASE 5). — Numerous Haversian canals, each surrounded in whole or in part by bone lamellæ, lime-containing hyaline connective tissue intervening.

FIG. 6 (CASE 4).—High-power microphotograph, showing the indentations and cavities within the lime-containing area. These contain a blood vessel, fibrillar connective tissue, and a few fibroblasts. All these structures are more mature than in Fig. 5.

FIG. 8 (CASE 4).—Low-power section taken near the periphery of the bony nodule. Shows space within the lime-containing area filled with delicate fibrous tissue, fibroblasts and young blood vessels. Along the circumference of these spaces are fibroblasts which have penetrated into the surrounding lime-containing tissue, which reveals a coincident lime absorption.

FIG. 7 (CASE 4).—From the interior of a bony nodule within the ovary, showing bone lamellæ, Haversian canals and bone-marrow.

FIG. 10 (CASE 5).—High-power; shows an Haversian canal surrounded by a narrow zone of bone lamellæ.

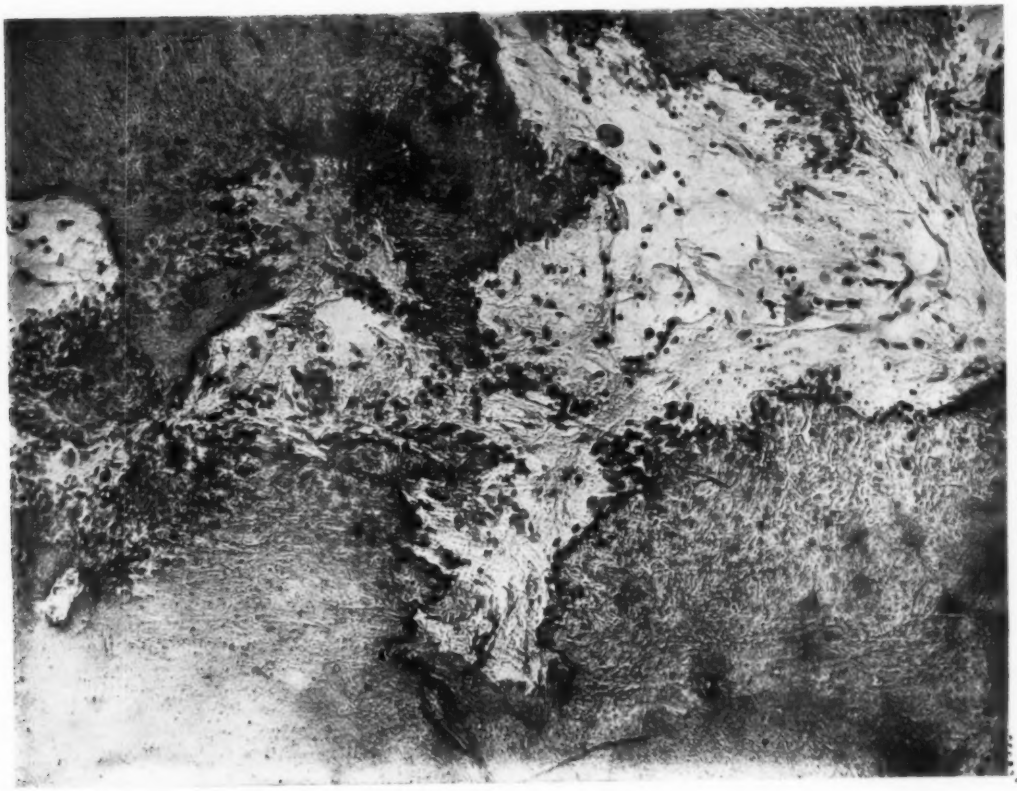

FIG. 9 (CASE 4).—High-power of Fig. 8.

fibroblasts is not so easily settled. In ossification of the ovary, these fibroblasts can have only two sources of origin: (a) the endothelium; and (b) the connective-tissue wall of the penetrating blood vessel. Inasmuch as we have shown that fibroblasts later become endothelium, the presumption is strong that the process in its earlier phases is reversed and that, therefore, these fibroblasts are, entirely or in large part, derivatives of the vascular endothelium of the penetrating blood vessel. In embryos, as Huntington, Schulte and others have shown, and in granulative tissue, as W. C. Clarke has demonstrated, these fibroblasts arise not only from the endothelium of the preformed vessel, but also, but in a smaller measure, from the fixed connective-tissue cell. As the hyaline connective tissue in which the lime is impregnated contains no fixed connective-tissue cells whatever, in our series this origin can be excluded.

However, the problem of the exact origin of these fibroblasts is of academic interest. For our purposes, their ultimate fate is a greater issue. As we have shown in our series, the fibroblasts assume three different functions: (1) as vascular endothelium; (2) as osteoblasts; (3) as constituents of the bone-marrow of the subsequent Haversian canals.

In the genesis of ossification their functions as osteoblasts is manifestly the most important.

A study of Figs. 3 to 8 can leave no doubt of the origin of osteoblasts from fibroblasts. In every physical property they are identical with the fibroblasts in their immediate vicinity. Here we note another instance of the close analogy between normal and abnormal ossification, for in developing bone the same origin of osteoblasts is accepted (Stöhr).

The exact manner whereby osteoblasts succeed in converting a calcified hyaline matrix into bone-plates is a matter entirely of speculation. Certainly histological data furnish no clue. In all probability, the influence is a physico-chemical one, a process covered with indifferent satisfaction by the term "metaplasia." Speaking in terms of histology, the process may be described as the following. Osteoblasts are arranged along the edge of the subsequent Haversian canal, which at this stage is bounded by a wall consisting of a calcified matrix of hyaline connective tissue. These osteoblasts penetrate for a greater or lesser distance into the lime-containing area (Fig. 9). The areas where osteoblasts are found stain much lighter than other areas, indicating a coincident lime absorption. Whether this absorption is due to activity of the osteoblasts or to a chemical action of the juices brought by the newly formed blood vessels, cannot be determined. At all events, soon after the penetration of the osteoblasts, bone-plates are deposited around the circumference of the future Haversian canal. This deposition is eccentric. As the bone-plates form, the osteoblast is converted into a bone cell.

The only detail in the histological picture that now calls for elucidation is the further development of the Haversian canal. As we have seen in Figs. 2 and 3, these are first represented by cavities or indentations on the surface of the lime-containing area, filled with a fine fibrillar connective tissue, fibroblasts and a blood sinus. In the next stage (Fig. 4), the blood sinus has become a frank blood vessel with an endothelial wall. The fibroblasts are more abundant and the fibrillar connective tissue is coarser. The subsequent changes (Figs. 5, 6 and 7) show a gradual senescence of these elements. The blood vessel is accurately shaped and is composed of a firm connective-tissue wall with a distinct lining of flattened endothelial cells. The fibrillar connective tissue is coarser, the fibroblasts are more abundant, the cell bodies and nuclei are more precise in outline, and the chromatin network is richer. The osteoblastic arrangement of the cells is more pronounced. Finally (Fig. 8), we have the mature Haversian canals with all their elements attaining their fullest fruition. In addition, we find that some of the connective tissue has undergone fatty change, and we find abundant round cells of the lymphoid type. In other words, the resemblance to the normal Haversian canal of normal bone is now complete.

A curious feature of ossification is the eccentricity of the process, the reverse of what we should expect from the concentric mode of development of the new blood vessels. This phenomenon is the counterpart of that occurring in the development of normal bone, in which we find the ossification proceeding from "centers."

Nature of Ossifying Stimulus.—There still remains the question as to the nature of the stimulus that converts a calcified tissue into bone. We must presume there is a stimulus, because not all foci of calcification turn into bone. It is nevertheless still debatable whether ossification is not an invariable consequence of calcification, given a sufficient period of time. Certainly pathological data indicate that ossification is the rule rather than the exception. For instance, Poscharisky [14] found bone in all but four of 29 cases of calcification of the eye. Of 28 calcified nodules in the lung, 17 contained bone.

Lick [15] produced bone experimentally in the pelvis of the rabbit's kidney as early as 16 to 20 days after ligating the artery, provided that the kidney was wrapped in omentum to secure a free collateral circulation. Without the collateral circulation, the process required three months. With too free a circulation, therefore, there occurs no calcification or ossification; with too little, necrosis occurs, followed by slow calcification, and either a late or no ossification. Apparently, therefore, a fine adjustment of blood supply is an important factor in abnormal bone production.

Wells believes that the stimulus is probably a tactile one, due to the presence of calcium salts. This is supported by the experiments of Barth,[16] who healed bone defects by introducing lime or dead bone, whereas, on the other hand, ossification was not stimulated by the introduction of decalcified bone.

The stimulus is undoubtedly a physico-chemical one, but the precise circumstances suggest an interesting field for future study.

SUMMARY.

A. Three cases of calcification and two of ossification of the ovary are described. The process in each instance involved a corpus albicans. The specimens represent an apparently continuous series, in which four stages are recognizable: (1) an early discrete multiple deposit within a healed corpus luteum; (2) a definitely circumscribed deposit of amorphous lime

within a corpus albicans; (3) the formation of primary Haversian canals—which is accomplished by the genesis of an active mesoblastic tissue, both upon the surface and within the interior of such a circumscribed lime deposit. This mesoblastic tissue is derived from the adjacent blood vessels of the ovary, and the predominant activity is the development of new blood vessels. Associated with this activity is the development of osteoblasts from the mesenchymal cells; (4) true bone formation—with maturation of all the elements described above, together with eccentric deposition of bone-plates around the primary Haversian canals and the formation of marrow.

B. The development of new blood vessels affords the keynote to the interpretation, in terms of cellular ontogeny, of the process of ossification. The histological constituents which enter into the formation of new blood vessels are the progenitors of all the histological components of osseous tissue. In other words, blood vessels, osteoblasts, bone cells and marrow (in large part at least) are merely differentiations of the mesenchymal cell unit.

C. Our specimens furnish strong corroboration of the "adaptive" or "mesenchymal" theory of angiogenesis, and to the theory of the non-specificity of endothelium.

D. Ossification does not occur without preliminary calcification, and calcification occurs only in dead tissues.

E. There is no valid reason for regarding bony structures within the ovary as blastomata.

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THE PRESSURE OF BILE SECRETION DURING CHRONIC OBSTRUCTION OF THE COMMON BILE-DUCT.*

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It is frequently observed in animals with experimental obstruction of the common bile-duct that a rupture of the bile passages may occur with escape of bile into the peritoneal cavity. The following experiments were undertaken to ascertain whether, following an obstruction, there is a rise in pressure within the bile passages from day to day.

A paper by Herring and Simpson [1] gives figures for the dog, cat, rabbit, and monkey. The animals were all put under the influence of an anæsthetic and the experiments lasted but a few hours at the most. The pressure in millimeters of bile varied in cats from 210 to 375, with a mean of 304.4; in dogs from 243 to 342, with a mean of 300. These observers found that stimulation of the vagi caused a somewhat prompt fall in bile pressure. Our experiments show no constant reaction following vagus stimulation, and it is possible that the explanation of this difference lies in the duration of the obstruction.

METHOD.

The animals were anæsthetized with ether. Under aseptic conditions the common duct was ligated with silk thread as near the duodenum as possible. In two cats the duct was cut. The animals were allowed to recover from the operation, and were given food and water. At the time the pressure was to be recorded they were again put under ether. A glass cannula was inserted into the common duct, which was clamped above this point. A vertical glass tube containing a solution of 1/10 of 1 per cent sodium carbonate or sodium hydrate was connected with the cannula by means of a rubber tube. The fluid in the glass tube was adjusted to the probable pressure level and marked. The clamp was then loosened very slightly to give a slight rise or fall, and the tube raised or lowered to meet it. Final adjustment with the meniscus at the mark on the glass tube having been easily made in this way, the glass tube was fixed in a burette stand, the clamp was completely removed from the common duct, and readings were made at frequent intervals during the experiment. The pressure was determined in millimeters, the measurement being made between the top of the fluid column and the level of the junction of the common duct cannula. The abdominal wound was then closed tight, but the anæsthetic was continued to the end of the experiment, when the animal was sacrificed before it had recovered consciousness.

The pressure was taken in 12 cats, and ranged from a minimum of 236 to a maximum of 360, with a mean pressure of 278 mm. The pressure remained remarkably constant, not

*This paper was completed during the year 1913-1914, but publication was delayed because of its transportation to the Pacific Coast. [G. H. W.]

[1] Herring and Simpson: Proc. Roy. Soc. London, 1907, LXXIX, 517.

rising or falling more than a few millimeters during several hours. The column of fluid usually rose and fell a millimeter with respiration, but in the case of the cat giving the highest pressure it varied 5 mm. with breathing.

We obtained no uniform variation in bile pressure by the stimulation of nerves. Electrical stimulation of the right vagus gave an increase in pressure in five animals with a maximum of 5 mm. The stimulation of the left vagus caused a rise in two and a fall in one of 4 mm. When the column of fluid was reduced to one-half, stimulation of either vagus caused sometimes a rise, sometimes a fall. The maximal change was a rise of 33 mm. with stimulation of the right vagus. The maximal fall was 3 mm., also caused by stimulation of the right vagus in another cat.

TABLE I.

Cat No.	Weight in lbs.	Days after operation.	Bile pressure in millimeters.	Dog No.	Weight in lbs.	Days after operation.	Bile pressure in millimeters.
2	...	2	244	1	15	2	278
5	7	2	284	2	17	2	†292
7	7.5	2	257	..	..	..	...
14	8	2	*292	..	..	..	...
15	8	2	†270	..	..	..	...
3	...	3	297	..	..	..	...
9	7.8	3	290	..	..	..	...
13	7.3	3	267	..	..	..	...
10	11.8	5	236	..	..	..	...
12	6	5	360	..	..	..	...
8	8	6	260	..	..	..	...

* Given 100 cc. pig's bile on the day after operation.
† Barium chloride produced a slight rise in pressure.
Average pressure in cats after two days, 269.4 mm.; after three days, 284.6 mm.; in all experiments, 277.9 mm.

Stimulation of a sensory nerve, the saphenus, caused a slight rise in pressure in four animals, with a maximal change of 6 mm.

Injection of epinephrin caused no change in pressure. Section of both vagi caused no change. Bleeding the animal or injecting normal salt solution caused no change.

The pressure was taken in two dogs in which the common bile duct had been occluded two days, and was found to be 278 mm. and 292 mm., respectively. The dogs did not show any difference from the cats, except in the lower pressure in proportion to body weight. Stimulation of the splanchnics of Dog 2 did not cause any change in pressure.

Injection of 0.25 cc. of a saturated solution of barium chloride was tried on one dog and one cat. In the cat there was a rise in pressure of 3 mm. after each of two successive injections; in the dog there was a rise of 5 mm. after the first injection and 2 mm. after the second. Smaller doses produced no change. This dose proved fatal in each case after the third injection.

Why do the obstructed bile passages so often rupture after an interval of several days? Not because of any continued and progressive rise in the fluid pressure within them. Perhaps the best explanation takes into consideration the inflammation which may occur to a greater or less degree even after aseptic operations. The rupture may occur close to the ligature on the common duct, in one of the fissures between the liver lobes where the ducts are close to the serous surface, or in some part of the gall-bladder.

These experiments show that in chronic obstruction of the common bile-duct the pressure rises no higher than in acute obstructions. It may be even higher at the end of three hours than at the end of three days, but probably there is little variation. There are individual variations which we do not attempt to explain. There is no relation between the pressure and the weight of the animal.

It seems relatively safe to assume that the pressure rises sharply during the first three hours after obstruction. After this time the pressure remains fairly constant, but is the resultant of two factors: (a) secretion by the hepatic epithelium, (b) absorption by way of the hepatic veins. Whether the bile escapes by rupture of bile canaliculi, or by diffusion from the distended channels, is an open question, but it is known that the bile pigments and probably the other elements of the bile are removed from the liver of obstructive icterus by the blood vessels rather than by the lymphatics, which play an unimportant rôle (Whipple and King).[2]

We may say with considerable certainty that there is a given pressure for each animal, usually between 250 and 350 mm. of water, at which the secretion and the absorption of bile are in equilibrium. In whatever manner this chronic biliary obstruction may react on the liver cells, it does not greatly influence the pressure within the ducts.

[2] Whipple and King: Jour. Exp. Med., 1911, XIII, 115.

WILLIAM TULLY, OF CONNECTICUT, 1785-1859.

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During the last years of the eighteenth century and the early years of the nineteenth there was great medical activity in Connecticut following the religious and political excitement of the Revolutionary days. It has been said that Nathan Smith, William Tully and Jonathan Knight were then to Connecticut, as doctors, what Ellsworth and Trumbull and Sherman were as statesmen. There were, indeed, at that time false prophets among the doctors, like the Perkinses and Thomsonians, but, on the whole, the medical affairs of Connecticut were guided steadily toward the establishment of the State Medical Society in 1792, and the founding of the Yale Medical School in 1813, after which her physicians became leaders in their profession in the United States.

Many of Connecticut's early practitioners had not received much medical education, and very few had studied in Edinburgh, like some of the Boston doctors, but they were what Cotton Mather called "Angelical conjunctions of Physic and Divinity." These "philotheologiatrónomoi" exercised their

skill in matters spiritual as well as physical, although being farmers they often had to plough or make hay by daylight, and visit the afflicted at night. There were both Whigs and Tories among them, and during the Revolution they had taken their share of military service as commissioned army surgeons or colonels, with the same zeal as they showed later in the War of 1812. Thus they knew no idle hours, for, although most of the large towns were situated on the Sound or on rivers, where travel by water was easy though tedious, the philo-theo-medicos almost lived in the saddle, carrying a Bible and medicines in dirty saddle bags, and reading, if it was daylight, "every known author." In addition to all these occupations, men like the great Dr. Nathan Smith carried on an itinerant medical school, teaching their pupils botany and materia medica by the roadside, and instructing them in surgery and therapeutics by the bedside of the patient. It was in this way that William Tully, the subject of this paper, studied with Dr. Smith, in 1808 and 1809, not only learning how to use setons and cups and leeches, the actual cautery and blisters and the lancet, surgical instruments and drugs, but also taking an interest especially in the diagnosis of diseases.

Of William Tully's ancestors we know very little except that they had lived for generations at Saybrook, on Long Island Sound, having come from England in 1647. One of them is mentioned in the Chronicles of the Pilgrims because "he like to have sounded with cold," and was in danger of scurvy. Tradition tells us that the Tullys, or Tillys, were noted for their skill in fighting the Indians; and we may infer that some of them were "natural doctors," for a Tully is said to have made the profound remarks, "no one ever sneezes in a settled fever," and "no one ever catches cold unless he catches heat first"; their remedies for these diseases being hot saffron tea, bloodletting, and a few Indian medicines.

Our William Tully's father was Colonel William Tully, a Revolutionary soldier, who married his cousin Eunice Tully; by this close relationship, it has been suggested, we may account for the irritability and idiosyncracies of their only child, who was born in 1785. That the boy was delicate we learn from a letter of his daughter in which she says: "My father barely lived for 20 years. He was trained for college by Parson Hotchkiss, but he did not succeed in arithmetic, and failed to take the valedictory on that account. In all other subjects he was the smartest in his class." This, unfortunately, is all we know of William Tully's early life, but from various sources we gather the essential data of the subsequent years.[1]

In 1806 he graduated from Yale College and began teaching in the Oyster River School, near his home. The terms were not long, and during the next two years Tully alternately taught in district schools and "read medicine," while collecting an herbarium from the fields and meadows in the country near at hand. The first medical teacher with whom he took any definite work was Dr. Mason Fitch Cogswell,* of Hartford, a famous physician and surgeon, who was said to have once amputated a thigh in 40 seconds.

In 1808 and 1809, as we have seen, Tully studied medicine with Dr. Nathan Smith in Hanover, New Hampshire. Of these years we hope to have the details when his diary is published. The following year Tully was again teaching school in Saybrook and studying with Dr. Samuel Carter, while at the same time he was taking a course in materia medica with Dr. Eli Ives in New Haven. It was this last subject which determined his career, because of his fondness for botany and his delight in Dr. Ives' wonderful garden of medicinal plants.

In 1810, his medical courses finished, Tully obtained a license to practice in Connecticut, and he was "called" to Enfield to begin his life work. He at once fell in love with Mary Potter, a doctor's daughter, but an attack of typhus fever debilitated him so much that he had to go home to recuperate. There he found his father dying, the family affairs needing attention, and so many questions to settle after his father's death, that his marriage was postponed until 1813. At that time he accepted an invitation to settle in Milford with his bride; but practice was slow in growing, and Tully spent more time in the fields, botanizing, than with patients; so that after two years of professional discouragement, they moved to Cromwell, which seemed more promising. This was in 1815, and it marked the beginning of Tully's success as a physician. His colleagues recognized his superior ability, and patients praised his skill. Three years later, cheered by these experiences, he decided to move to Middletown, a few miles down the Connecticut River, which at that time was one of the largest cities in the state.

While practicing in Middletown, 1818-1824, Tully attained considerable distinction as a physician and was much sought for as a consultant. He was at once appointed clerk of the County Medical Society (founded in 1792, one month earlier than the State Society), but we find only one record signed by him. This entry was dated 1818; it is simply: "Voted to adjourn to the parish of Potapaug in Saybrook, to the house of Danforth Clark, or to the next nearest tavern, or to the meeting-house in said parish." Nothing could be more concise. He was also appointed to "perform" at one of the meetings, but there is no record of his performance. We find, however, that the topic of church going was discussed about this time, and it was solemnly voted that the members should endeavor to attend public worship on Sundays. Moreover, it was voted that the society should not use ardent spirits at its dinners; thus signifying its disapproval of alcoholic beverages, a great step in those days when at each house a doctor was expected to have a drop of whiskey before seeing the patient. This prohibition motion was, perhaps, made by Tully, for his daughter, in a letter says: "My father never used tobacco, he despised it and whiskey too. He never took whiskey only when he came home very tired, and he always talked temperance."

The year after Tully settled in Middletown he received an honorary degree of M. D. from Yale College, where his medical teachers, Dr. Smith and Dr. Ives, were now professors. The following year, 1820, he published in the *Middlesex Gazette*

* Dr. Cogswell is remembered as the founder of the Hartford Asylum for the Deaf and Dumb, now known as the American School at Hartford for the Deaf.

his first long medical article. This was on the subject of scutellaria and its alleged curative effects in hydrophobia. In a rather dramatic manner he recites the history of a young girl of 14 years, named Mary Tice, who had suffered for 20 months from an unhealed wound of the hand. Then, suddenly being taken ill with fever and vomiting, she told her parents that a black dog had bitten her hand. Seeing their consternation she began to bark and to "go into convulsions at the sight of cold water." Many doctors who saw Mary in these attacks "gave her up," because she could swallow none of their medicines. Finally a new doctor saw her, bled her freely, administered 60 grains of calomel, soon had her drinking a quart of an infusion of scutellaria every 24 hours, and cured her in 6 weeks. Tully gives this story in more than 7400 words, printed in eight long columns of fine print, and he argues that since there was no authentic medical testimony that Mary Tice had hydrophobia, and since scutellaria had never been proved to have any medicinal value whatever, his own diagnosis is that the child had hysteria common to her age. This gives him an opportunity to hurl invectives at physicians who rush madly after new and untried remedies, and to condemn all newspapers which publish sensational but unauthenticated reports of cures of extraordinary diseases by newly discovered drugs. Toward the close of the article Tully, with ill-concealed sarcasm, offers to drink three pints of infusion of scutellaria every day for a twelvemonth to prove that it is as inert as common Bohea tea, and he advises the laity to keep scutellaria among the safe and common dried plants in their garrets, along with mint and mother-wort, sage and catnip.

Soon after the preceding article was published Tully was appointed to read a dissertation before the Convention of the Connecticut Medical Society at its meeting in 1822. His topic was "The Yellow Fever in Middletown in 1820." This dissertation formed a portion of the *Essays on Fever*,[2] published in 1823, by William Tully and Dr. Thomas Miner, one of his colleagues.

There had been 35 cases of yellow fever in the lower Connecticut Valley in 1820, fifteen of which had been in Middletown, caused, it was thought, by decomposing vegetables and filth from a vessel at anchor at one of the wharves. Tully, however, was not satisfied that the origin of this disease had been found, and he says, "The causes of the rise, progression, diffusion, and final extinction of epidemics are, in our opinion, involved in impenetrable obscurity—at least in the present state of medical science. We hope that the period will soon arrive when the medical profession will no longer esteem it an evidence of wisdom to affect to know what they are in fact ignorant of, and to consider themselves as bound in duty to supply by hypothesis what they lack in knowledge." (p. 459.) And again (p. 348): "Yellow fever will forever remain one of the most unmanageable and fatal of diseases to which mankind is subject. . . . . For, since it is a part of the scheme of Providence that men shall continue mortal, it is probable that epidemic diseases will ever be a great instrument in producing this mortality." In this confession of ignorance Tully was in accord with Dr. Nathaniel Potter, of Maryland, who, in 1817, after trying in many ways to take yellow fever from his patients, said: "It comes, they know not whence; and goes, they know not where. Pursue it as they may, it must still elude their grasp, vanish with circumambient air, and like the baseless fabric of a vision, leave not a trace behind."[3] There had not been such skepticism as to the causes of contagion when Tully was a boy, for Noah Webster, in 1794, had proved to his own satisfaction, and apparently to that of the world, that an epidemic in New Haven was caused by "decaying shad which had been thrown into the dock," to which was added the odor of rotten clams and of a barrel of pickled codfish uncovered at low tide. But 25 years allow time for great changes in medical ideas, and, while doctors agreed with Currie, of Edinburgh, that contagion spread by laws peculiar to itself, they hardly dared accept the theory that it was an airborne disease, and abandon quarantine against it.

Therefore, obliged to leave undiscovered the causes of fevers, Tully discusses their symptoms, and for the sake of simplicity in treatment, he divides all fevers into two classes. These are "putrid fevers, including jail, ship, or hospital fever, which bear bleeding well," and nervous fevers, including spotted fever and pneumonia, "in which bleeding would never be tried but for the rash surgeons, who since the war of 1812, had bled all their patients." For these latter fevers Tully strongly advises against using any depleting measures, such as, for instance, an emetic repeated as often as a patient stopped vomiting. He quotes one case where 70 grains of tartar emetic had been given until the patient was almost dead, and this was followed by as large doses as the stomach would bear of cinchona, camphor, sulphuric acid, ammonia and ether.

"Dashing practice" was evidently the order of the day. Tully says, "The lancet has annually slain more than the sword, and antimony has done more injury than all the efficient exciting and supporting agents of the materia medica. The King of Britain loses more subjects each year from these two causes than the campaign of Waterloo cost him." (p. 461.) But even Tully was as extravagant himself in the use of "exciting agents" or "stimulants" (?), among which were calomel and opium. As regards these drugs he believed that the timid physician was the patient's worst enemy; and he tells his readers how to give these remedies: "More than 1000 grains of calomel may be given in the preparatory stage of yellow fever, and a proportional quantity of mercurial ointment applied externally, not only with safety, but with the most complete success, for neither weight nor measure is to be at all regarded till there is an alleviation of the disease." But he adds: "If calomel is not given in the first stage of the disease, it should not be given at all." (p. 335.) As to the use of opium, it was to be given "steadily, resolutely and perseveringly, at short and regular intervals, in such quantity as to allay all the pain and irritation, and to support the powers of life." (p. 329.) As to the dosage, he says, "It requires not more than seven or eight grains of opium in 24 hours to keep 100 grains of calomel from running off from the bowels." He often gave 60 grains of calomel the first day in the form

of a syrup, "not desiring to cause ptyalism by the mercury or a soporific effect from the opiate," as, in fact, he had noticed that the opium often mitigated coma or stupor. If any physician doubted that this was the very best treatment of fevers, Tully considered him "timid, desultory and skeptical, and not able to make observations with sufficient accuracy to gain any useful experience."

In the use of alcohol it would seem to us that Tully was even more "dashing." "To the sunken cases," he says, "I give great quantities of spirits. . . . . From two pints to a gallon of whiskey in the 24 hours, with the happiest results." He adds that he has never known intemperance to be caused by any spirits given in sickness, but he says, "I believe that the liquor of the arsenite of potassa in half-drachm doses would have done as well, or laudanum in drachm doses every half hour for several days."

In the light of the twentieth century we are not surprised that the advocacy of such dosage, even in contemporary times, brought forth much adverse criticism of Tully's therapeutics.* But criticism he never could endure, and so great was his irritation at the unfavorable comments of his colleagues that he was unwilling to live in Middletown among them any longer; consequently, in 1824, we find him settled in East Hartford where he already had many friends in the profession. Here lived his first teacher, Dr. Mason Fitch Cogswell, who had declined the chair in surgery at Yale, and Dr. Eli Todd,† the founder of the Hartford Retreat for the Insane, and many another choice spirit. Together they formed a social club in memory of that "wit among poets and poet among wits," Dr. Lemuel Hopkins, who had died in 1804. They took their wives with them when attending the meetings of this club, often riding 10 or 15 miles on horseback to the homes of the various members.

In the society of such congenial colleagues Dr. Tully should have been contented, but, having accepted the chair—"settee" rather—of materia medica, and theory and practice of medicine, besides the presidency of the new Vermont Academy of Medicine, at Castleton, a few miles south of Rutland, he was obliged to be there for 14 weeks each year. This enforced absence caused grumbling and criticism among his patients and colleagues in East Hartford; and the ever intolerant Tully, in less than two years, decided to move to Albany. His wife, although somewhat of an invalid, had borne him eight children, of whom six had died in infancy. History fails to tell us how she liked these uprootings, but most wives were patient in those days, and therefore to Albany they went, where the doctor became a partner of Dr. Alden March. This arrangement lasted, however, only three years, for in 1828 Dr. Tully received an invitation to fill the chair of materia medica and therapeutics at Yale, made vacant by the resignation of Dr. Ives. He accepted the call, and the family moved to New Haven in 1829. The following year twins were born to them, making 11 children in all, of whom only four lived to grow up. These children were educated in New Haven, their home for 20 years. During 14 of these years Dr. Tully lectured both in Castleton and New Haven, having larger classes in each of these schools than were found in any other institution in New England. Moreover, it was said that most of his advanced students "worshiped him"; but the younger ones found great fault with his style, and they criticised him so continuously that he felt that he was wasting his time in trying to teach them. Tradition tells us that, dissatisfied with his compensation, and irritated at the never-ending agitation against him by colleagues and patients as well as students in New Haven, Tully handed in his resignation about once a year, until finally, in 1841, the authorities at Yale accepted it, probably much to his chagrin.

What these criticisms of pupils and colleagues and patients were, we find in an account of the life, as a Yale medical student, of Dr. F. W. Mathewson, of Durham, who was graduated in 1833, in a class of 69. He tells us that the proems to Tully's descriptions of drugs were too long and tiresome; that one lecture often filled 90 pages; that his repetition of Latin words and phrases made the taking of notes difficult; but, notwithstanding this verbosity, and an irritating vehemence in denouncing popular treatment by the lancet, and antimony and other reducing agencies, the older students found him interesting, and they learned more practical medicine from him than from any other teacher. Tully's colleagues also found fault with him for his denunciation of their "dashing treatment." And, one by one, his patients turned from him to more tactful, if less learned doctors, and his colleagues even refused to have him in consultation because he had so frequently said that he preferred to talk himself rather than to listen to their "prattle." He often spoke disparagingly of patients' "garrulity," and called it "medicina anilis." Moreover, other members of the faculty thought his courses too severe in comparison with theirs. We wonder what some of the other courses were, for there were none at all in organic chemistry or urinalysis, or in auscultation and percussion; and only half a dozen lectures in gynecology with no demonstrations of the vaginal speculum. The microscope was new and to be looked at, not through. The new hospital furnished no clinical material, and the use of the fever thermometer was not considered worth while for the occasional patient. On the other hand, surgery was well taught by Dr. Nathan Smith, and anatomy was elucidated by means of an occasional body snatched from the grave, and, according to Dr. Smith, "hewn in pieces as Samuel hewed Agag, but for a different reason." Therefore, if Tully's courses seemed severe, it was because of his breadth of vision. He meant to impress his pupils with the necessity for exactness in prescription writing and compounding. It was important for them to know Latin, the universal medical language; and it was a *sine quâ non* that they should

* Forty years later Oliver Wendell Holmes said, "Dr. Hooker believes that the *typhus syncopalis* of a preceding generation in New England, was often in fact a brandy and opium disease."[4]

† In 1822-1824 Tully was one of a committee of three that drew up the Constitution of the Hartford Retreat, pushed the bill through the legislature, and raised the money to start the Institution. Dr. Todd was the chairman of the committee, but Tully's energy was needed to supplement the pathos and logic of Todd's oratory.

not combine incompatible drugs or prescribe "shot-gun" doses.

Surrounded as Tully was, therefore, by so many opponents, and convinced that his compensation was in every way too small, he can hardly be blamed for resigning his position at Yale. We do not know what his salary was, for it was paid directly by the students at $12.50 per capita, and from other funds of which no record remains; but it could hardly have been less than that which Dr. Smith received for his courses at Bowdoin College, which was $100 a week for a six weeks' course. As for medical fees, Dr. Smith said: "The people of Connecticut have no idea of rewarding professional men except by compulsion or by being begged. The lawyers compel and the priests beg for pious purposes." The usual charges for medical services, however, were "two shillings for a day visit, four for a night visit, one for a mile travel, one for a puke, one for a purge, one for bleeding," etc. These charges always included all necessary medicines prepared by the physician.

Having, therefore, lost his salary from both Yale and Castleton (where he had resigned in 1838), and not being afflicted with too many professional fees, Dr. Tully was undecided what to do next. He had already begun to suffer from some affection of the bladder which caused his death 19 years later, and therefore the state of his health may have prompted him to go to Charleston in 1842, possibly to settle there if everything should be to his liking. He had refused a call to the University of South Carolina in 1833, where he may have still had friends, but there seemed to be no opening at this time in that warm climate; and so, disillusioned once more, he went back to New Haven the next year to pick up what practice he could and prepare his "briefs" for publication. Finally, in 1851, the family moved to Springfield, Massachusetts, where these briefs of his monumental work, the Materia Medica, were to be printed.

It was in Springfield, in 1853, that Dr. Tully's wife died; and he himself, in 1859, "plenus annis, ex hac vita migravit." He left a small estate to his three surviving children, but his library of 2000 volumes and his instruments were sold at auction for a small sum, "a mere song," his daughter says; and, as his manuscripts had no pecuniary value, they were given to one of his students. Two volumes only of his great Materia Medica were finished, and they were too encyclopedic to sell profitably.

Discouraged with life, a short time before he died Tully had said: "It is well known that the emoluments of the medical profession are by no means in proportion to the amount of work done, and as for medical schools in New England, they diminish rather than increase the income of the instructors; at least such has certainly been the fact as concerns myself, for I have wasted my time 16 years in one institution (Castleton), and 14 in another."

Such, in brief, are the main facts in the life of William Tully. One of his friends, Dr. Miner C. Hazen, gives us this picture of him: "Tully was a large man, tall and broad, with a wide head and prominent eyes, and would have been a man to attract attention anywhere without the gift of speech. I remember him well as he used to fill the large armchair in H. J. Brewer's drug store, in Springfield. He seemed to be perfectly happy if he could get a doctor or two to listen to some of his learned talk, generally on some article in the materia medica. At such times he did all the talking in a loud voice with an assured manner. The world itself could hardly have held all the books he would have written if he had had the opportunity."

Of the accompanying portraits of him, Tully's daughter says: "The lithograph was considered very good when he lived in Hartford, and the daguerreotype was a fine likeness of the noble man." Continuing her remininscences, she says: "My father was a very warm-hearted man and thought a great deal of his family. He had no hobbies and no musical talent, he rather laughed at such things, but he was fond of poetry and would read it beautifully; he never cared for any other recreation, only reading. He loved children and would trot them on his knee, and they always expected it and called him 'docor.'"

From contemporary writers we may also draw an imaginary picture of Tully as he went on his professional rounds. He always carried in his vest pocket a small bunch of papers which he called "octets." Wherever he was, on the street or in the sick-room, if a thought struck him he wrote it down at once on an octet, whether he interrupted a patient's tale of woe, or was dosing a child for diphtheria with his favorite remedy, turpeth mineral. His study of drugs required careful notes at the bedside, and his lectures demanded of him great accuracy in recording the effects of his remedies. Therefore, he says: "If the dio-proto-sulphate of mercury does not operate in an hour, give ipecac to quicken it. The second or third act of vomiting generally brings up the membrane." Probably then, while the croupy baby was struggling for breath Tully was taking notes on this "most slandered drug," or pompously trying to impress the poor mother with his wealth of knowledge, for it is said that he could describe diseases with great unction, but sometimes fail to recognize them clinically. Perhaps it is well that he had no Boswell.

But if Tully had faults, he also had many virtues which scholars could appreciate. Dr. Bronson[5] said that he knew botany and chemistry better than anyone in the United States, and it was this knowledge which gave him an association with the early editions of the National Pharmacopeia. It had chanced that when Tully was taking his medical course with Dr. Nathan Smith, in 1808, Dr. Lyman Spalding was in Hanover, New Hampshire, agitating the question of a United States pharmacopeia. Tully was evidently impressed with the necessity for such a work in place of the clumsy formularies which each state had compiled for itself, and after he had finished his studies, while Dr. Spalding was bringing the subject before the medical societies of New York and some of the New England states, Tully frequently advocated the matter in Connecticut. Time was needed, however, to discuss the elimination of certain drugs which, though proved to have little value as medicine, yet had always been in the list, together with the long special prescriptions which had been handed down from past generations. At length, in 1817, the

New England societies voted to hold a conference in Boston, in 1818, at which delegates from all these societies and the medical schools should meet to discuss the question. From the members of this convention 12 delegates were elected to go to Washington in 1820, to compile a national pharmacopeia in one volume, according to the instructions they might receive from their own states or colleges. Tully was among the delegates to the conference in Boston, but he was not sent to Washington, and, therefore, he had only an indirect share in the preparation of the first edition. Ten years later, however, he was one of the 10 delegates who met in New York to revise the first edition "in accordance with the present advanced state of science."[6] This must have given him great pleasure, and he doubtless seized the opportunity to suggest substituting his camphorated opium powder for the old-fashioned Dover's powder, but we do not find it in the accepted list of formulæ.*

While in his prime, therefore, Tully must have led a busy life, but he found time to write a good deal for the medical journals, and among his articles we find the following titles: Ergot (1822); Datura, Sanguinaria (1828); Ferns growing near New Haven; Narcotine and Morphine; Actæa Racemosa; Chlorite of Potassa; and Congestion. For these articles, his daughter says, he was so "persecuted that he refused to publish others." Probably the persecution was nothing more than ordinary criticism, but, as we have seen, Tully did not take kindly to that sort of discipline. After retiring from such active work, however, he was persuaded to compile his briefs, and publish his masterpiece, the encyclopedic Materia Medica.[7]

The introduction to this work occupies 365 pages, the classification of drugs 83 pages more, and there were finished 1534 pages in all, a small part only of the contemplated work. This prolixity was due to the immense number of drugs which were supposed to have medicinal value. Tully said: "Even on the grounds of substitution an extensive catalogue may be not only useful but important, taking the circumstances of time, cost or availability into consideration." Surely Tully's ideals were high, for his motto was, "A doctor should never be satisfied until he knows everything that can be known." His plan was, then, to catalogue all the articles of the materia medica which the physician should have at his command, comprising, (1) "Every indigenous remedial agent which is definitely known to be capable of being useful in the treatment of any cases of disease; and (2) every exotic article of the same general character that can be conveniently obtained and easily kept."

Tully, we see, did not believe with Lord Bacon that a multiplicity of remedies is the child of ignorance, for he says (p. 295): "It appears to me that the educated, graduated, licensed, or as he is so fondly called, the regular practitioner, who habitually treats every variety of case of all species of disease, with a very few articles of medicine, is in no respect better than the uneducated, non-graduated, unlicensed and irregular quack, who does precisely the same thing." He scorned the great Abernethy's skepticism of drugs, and he says of him: "Apparently it would have given Mr. Abernethy no deep concern, if all the articles kept at Apothecaries' Hall had been washed away in a general deluge of pharmacy. The blue pill, Plummer's pill, the infusian of gentian and senna, and the decoction of sarsaparilla, were almost the only preparations which he would have admitted into the Ark."

As Tully's belief in drugs was firm, so he was strong and long in discussing them. He enumerates the effects of each one and gives the results of his experiments with it. As he did not believe in hypodermic medication, so he also scorns the idea of injecting medicines into the veins, especially "a pint of brine, an antiphlogistic cathartic which makes no part of the natural circulatory fluids." He says (p. 265): "This foolhardy operation could never be done by any physician in his senses." Nor does he think that a competent observer would conclude that experiments on animals could lead to any correct estimate of the effect of such drugs on human beings. There are many pages of lengthy arguments concerning proofs of experiments which do not stand the test of time.

In definitions, too, Tully was painfully discursive. He had defined many words for Webster's Dictionary (editions of 1840 and 1847), and these—anatomy, physiology, botany, for example—he had defined briefly and to the point, but in his Materia Medica he was not limited by time or space. Common oil of wintergreen is "Ol. Pyrolæ, a true saline æther, the spirhylate or oxyspirhylate of protoxyd of methygen, existing naturally in the plant Gaultheria procumbens." The word adenagic* is defined in one hundred and eighty words; the explanation of the action of drugs belonging to the class adenagica occupies sixty pages; and each drug in a class, such as mercury, the iodides and the bromides, also requires long discussions. Is

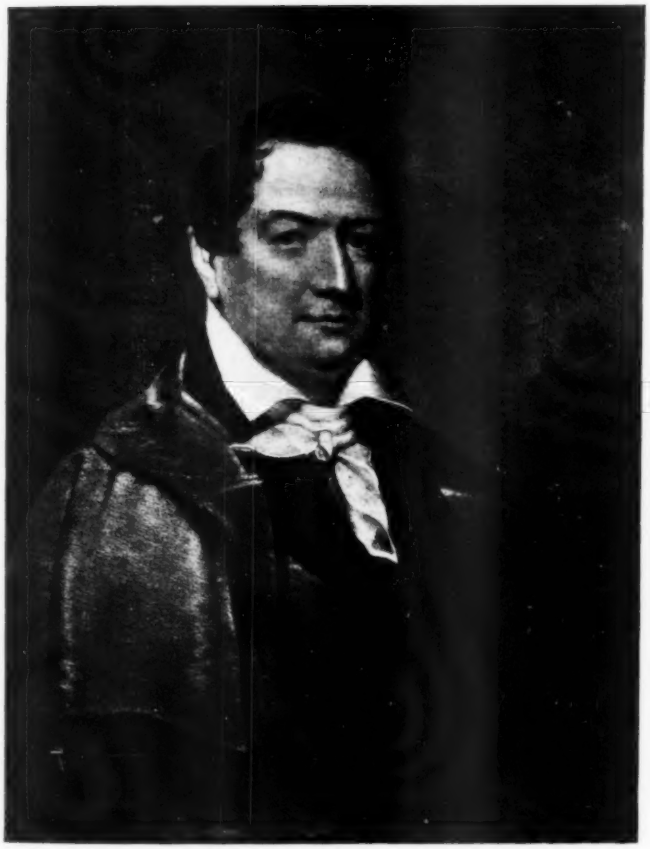
* The formula for the Tully powder was as follows:

Morphinæ oxydi sulphatis, gr. j	
Camphoræ officinarum,	aa gr. XX.
Radicis Glycyrrhizæ officinalis,	
Calciæ Carbonatis mollioris preparati,	

This powder was to be so divided that 10 grains contained 1/6 grain of morphine. For its preparation Tully gave minute directions, having no confidence in the judgment of doctors or pharmacists as to the quality of the ingredients or the care with which they should be mixed.

* Mat. Med. p. 1126, Vol. I, Part 2.

Definition.—Adenagics are articles which exert a direct, an especial, a peculiar and a specific operation upon the secernents and absorbents or the glandular system generally, by which a greater or less change of action and condition is produced—a change manifested by a direct resolution of certain chronic, subacute atonic phlogoses or inflammations; certain parabysmata and glandular enlargements; by the obviation of certain dysthetica; by the improvement of certain vitiated ulcers; by the relief or cure of certain cutaneous diseases; by the obviation of torpor and inactivity of all the secretories and excretories; and as is commonly said, though I think incorrectly, of the secretory apparatus of the liver; and by a consequent increase of the secretions and excretions, and as is commonly, but I think erroneously, believed, more especially of the biliary than of any other, and also by a diminution and improvement of the secretions and excretions where they are excessive and vitiated; the whole independent of any change in the degree of the vital energies or the strength of the action of the sanguiferous system, and not caused by any evacuation which may happen to be produced.



WILLIAM TULLY, M. D., 1827.

WILLIAM TULLY, M. D., 1785-1859.
(Taken about 1841.)

it any wonder that Tully's students had rebelled at the work he gave them if his book is a sample of his lectures? He stops in the middle of a long definition to condemn the general looseness of medical phraseology, and to berate the unscientific doctors who used words which their patients could understand. He insists upon calling catarrhal bronchitis "idiopathic blennorrhea bronchialis"; catarrh of the urethra, "urethritis pyo-blennorrhoica"; etc.; but for these many-syllabled diseases he tells us there is no cure, since there are no "true expectorants, apostethistics or chremptics." (p. 1259.) This was surely a disheartening avowal for those days, when there were few therapeutic nihilists, and fewer patients who did not expect to take large doses of medicine in order to be properly cured.

But however long-winded Tully was in his Materia Medica, and however egotistic in his treatment of disease, "The imperfections of the work are all forgotten," Dr. Bronson says, "by him who has the capacity to understand it." Even in our day it should be regarded as a classic in its unfinished state, and it is most unfortunate that the intervals of its publication were so often lengthened by the illness of the author, and that his death, in 1859, ended the work so abruptly. There was no one able to carry it through even with the "briefs," but the sales were not assured, and the few copies which had been sold are probably seldom used even for reference, although the work is full of interesting information collected from all over the earth.

It is idle to conjecture what William Tully might have achieved under more favorable conditions, although he is seen in truer perspective now than in his own times. We have seen enough, however, to show that he stood far above the rank and file of his contemporaries, for, as Dr. William H. Welch[8] has said, "He was a really remarkable man, erudite, original, an experimentalist unrivalled in his knowledge of the materia medica, and an extensive contributor to medical literature."

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

NOVEMBER 1, 1915.

1. **Exhibition of a Case of Benzine Poisoning.** R. L. HADEN.

This patient was admitted to the hospital on October 4, 1915, complaining of weakness and dizziness. He is 42 years old. His family and past history have no bearing on the present illness. Since July 14, 1914, he has been working in a lithographic establishment in this city, where he was employed in cleaning the lithographic rolls with benzine. In this work he has a trough about 6 feet long and 1 foot wide, filled with benzine, in which the long rolls are dropped and cleaned. He has worked at this for a variable number of hours, averaging about 5 hours a day. He has been using about 2 gallons of benzine a day, all of which evaporates. The work is done in a very large room, but to keep the lithographic inks from drying, the room is without ventilation.

After about 2 months of this work, he began to have quite severe nausea, vomiting and dizziness. The symptoms were progressive. About the same time he had a peculiar feeling in his head, which was not a definite headache, but what he describes as a "sense of compression" or "a pressing-in feeling." He was also getting weak. On account of these symptoms he left off work after two and a half months and went to a hospital in Washington, where he had been operated on three years previously. After staying there three weeks, the condition largely cleared up. He returned to Baltimore and went back to work. The symptoms rapidly returned and since that time he has been able to work only about 4 days a week. The symptoms have been as follows: He has had nausea, vomiting, dizziness and a peculiar sense of compression in his head continually. Later drowsiness developed. He was so drowsy that he often had to stop his work and wash his face in cold water in order to stay awake. There was a sensation of heaviness in his limbs, his legs feeling "like bags of cement." In addition, there was coldness in his legs, a feeling as "though menthol had been rubbed on them." He had some pains in his legs and arms, the pains in the arms being associated with a cramp of the muscles and ending in a marked hypertension of the fingers. He noticed also dimness of vision and twitching of the eyelids. Meanwhile, his weakness had become so extreme, that whereas formerly it had taken him only 15 minutes to walk from his home to work, it now took him about an hour. Very often, he says, he would feel as if he were walking, when, in fact, he was not moving at all. Several times he fell on the street. Five weeks before he came into the hospital, he noticed that his urine was becoming dark and had a peculiar odor. Two days before admission someone told him he was jaundiced. For some time he has been troubled with spontaneous contractions of the muscles of the legs and arms, which often awakened him at night. On account of these symptoms, he had to stop work on the 27th of September.

On admission, he was a fairly well-nourished man, but so dull that it was difficult to get a history from him. He seemed to be unable to speak or to think clearly. There was a very peculiar color to his lips, which seemed to be a combination of an intense cyanosis with the jaundice, giving a peculiar purplish tint. There was a peculiar odor to his breath, which did not resemble that of

benzine, but was rather sweetish. His lungs showed signs of chronic fibroid changes at the apices, without any evidence of activity. The liver was 2 fingerbreadths below the costal margin and tender on palpation. The spleen was easily felt. There was marked tremor of the eyelids and tongue. All the deep reflexes were extremely active, as were also the superficial reflexes, and there was a very marked contralateral patellar reflex. There were no clonus, fibrillary tremors or muscular atrophy. The plantar response was normal. There was no spasticity. On sensory examination, no change was made out. The blood examination showed 4500 white and 4,300,000 red blood cells; hæmoglobin 70%. The differential count was normal. Two gastric analyses showed a slight hyperacidity; the stool was normal; the urine was almost black with bile, and there was a trace of albumin. The Wassermann and Calmette (1% and 5%) tests were negative.

Since he has been in the ward he has cleared up mentally, and the cyanosis and jaundice have both disappeared. The peculiar odor of his breath has also entirely disappeared and there is perhaps some improvement in the condition of his nervous system.

It seems fairly clear that this is a case of chronic benzine poisoning. We think this diagnosis is fairly definite because of his long exposure to this substance, and the fact that his symptoms have twice cleared up shortly after he left his work.

In 1901, four cases of chronic benzine poisoning were reported from the medical clinic in Berlin. Four workingmen in a rubber factory presented symptoms similar to those in this case. There were nausea, vomiting, headache, dizziness, pains and sensations of heaviness and coldness in the limbs, with cyanosis and spontaneous contraction of the muscles. Jaundice was not described in any of these cases. However, there is one case of acute benzine poisoning reported, in which jaundice appeared in 24 hours. In two of the Berlin cases there was a peculiar change in the blood, free pigment appearing in the plasma and in the red and white cells. We have looked for free pigment in this case, but although we could note some in the plasma, we have not demonstrated it in the red or in the white blood cells. Dorendorf, who reported the Berlin cases, did a number of experiments on guinea-pigs, in which the animals were allowed to breathe the fumes of the benzine for short periods over a number of days. In these guinea-pigs pigment was found in the blood and a number of the symptoms referable to the central nervous system were present. On section, the guinea-pigs showed peculiar changes, mainly in the anterior-horn cells; these showed a deposition of pigment and a large number of vacuoles.

At the present time the patient still has rather marked tremor of his eyelids and some tremor of his tongue. He still has very active reflexes and a contra-lateral patellar reflex. At times, while he has been in the ward, when the triceps tendon was struck, nearly all the muscles of the body would contract in a manner very strongly suggestive of a convulsion from strychnine poisoning.

DISCUSSION.

DR. FUTCHER: On a number of occasions I saw this patient in the ward, and I do not think there is any question but that he is suffering from benzine poisoning. Owing to rather severe pain in the upper abdomen, the question came up, on admission, as to whether he might have some chronic trouble, in addition to the possible toxic manifestations. He had been in Cuba, where he had a dysentery, so we had to keep in mind the possibility of his having an amœbic abscess of the liver, although there were no physical manifestations. As he was jaundiced, we had to keep the possibility of gall-stones or chronic cholecystitis in mind also. I think Dr. Haden was strongly impressed from the beginning that we had to do here with a case of industrial poisoning, and Dr. Janeway, when he saw the patient a few days after admission, was also firmly convinced that his symptoms were essentially those of benzine poisoning.

If one reads Dorendorf's article in which the two cases are reported, and compares the symptoms with those presented by this patient, one finds they are practically identical with those described here. *Benzine* is not as pure a compound as *benzene* is. It is the same as benzol, but with a mixture of hydrocarbons. The symptoms and physical signs are rather different from those we get in true benzol poisoning. The drug seems to exercise a special influence on the nervous system and on the blood. There appears to be, in some of the cases, an actual oxyhæmoglobinæmia. Dorendorf found that the spectroscope showed the two characteristic absorption bands between the D and E lines of Frauenhofer's scale. Both patients presented these features. I do not know whether a spectroscopic examination was made in our case. The patient has been in the ward some time and it is doubtful whether the blood would show the changes at this time.

The striking features in this case were his physical weakness, mental hebetude, the cramps in the muscles, the nausea and vomiting, and the oppression in the head. The exaggeration of the knee-jerks was very striking from the beginning. A good many of the cases reported not only had the oscillation of the eyelids, but tremors of the muscles in general.

What causes the pains in the extremities is a matter of doubt. Whether or not they are in direct relationship to the changes in the central nervous system, I do not think has been definitely determined.

It is rather interesting, that in this hospital we have had several cases of benzol poisoning, with a fatal termination in two of the cases. Several of the patients recovered; the most recent case was here about a year ago, and recovery followed after several indirect transfusions. I think we have here the first case of undoubted benzine poisoning in the records of the hospital. Oliver, in his interesting book on "Dangerous Trades," has quite a long chapter on benzine poisoning. His cases occurred chiefly among workmen in powder and explosive manufactories in England, where benzine, particularly in its nitro compounds, is used in the manufacture of explosives. The symptoms present were very similar to those which this patient had, and which Dorendorf reported in his two cases.

DR. MILLER: There seems to have been a little doubt as to this case being one of benzine poisoning. There could be no doubt about the poisoning by kerosene in one of the first cases to be admitted to the Phipps Psychiatric Clinic. This patient, having made his escape, swallowed the contents of a bottle holding about two quarts and a half of kerosene before he was rescued, so there could be no doubt as to the lesions which subsequently developed. It is rather interesting to note that this patient, who presented a hypermanic type prior to the taking of the kerosene, lapsed into the extremest condition of hebetude. As he slowly emerged from this, he showed clinically, more or less, the symptoms described in this benzine case. He complained for a long time of the curious sense of oppression in his head. He could not walk, and, over a period of about six weeks, was definitely jaundiced. During that time the urine was extremely dark, and it showed the bands of oxyhæmoglobinuria when examined spectroscopically. Apparently the two poisons may be more or less analogous.

2. The Interpretation of a Positive Nitrogen Balance in Nephritis.*

HERMAN O. MOSENTHAL.

In the study of nitrogen metabolism, in certain cases of nephritis, a retention of this substance was observed. The conception of the retention of nitrogen in nephritis, as understood by the clinician, generally implies two facts: Firstly, that a marked positive nitrogen balance is usually due to kidney insufficiency; secondly, that

* From the Medical Clinic of The Johns Hopkins Hospital, Baltimore.

the retained nitrogen is present in the body as waste nitrogen and circulates in the blood, in part, at least, as non-protein nitrogen. It is known from the work of Marshall and Davis † that urea is evenly distributed throughout the body, except in certain tissues, as the fat, bone, cartilage, etc., which do not take up urea. In calculating the theoretical amounts of non-protein nitrogen to be expected in the blood, it has been assumed in the present series that all the nitrogen which the body has metabolized, and is about to excrete, in contradistinction to the nitrogen which the tissues are storing, is evenly distributed throughout the body, as is the case with urea. Applying these principles to the total non-protein nitrogenous products, it is found that in a subject of average weight, for every gram of nitrogen retained, the non-protein nitrogen of the blood should be increased 1.33 mg. per 100 cc. According to these calculations, in the cases presented here, if none of the retained nitrogen was assimilated or stored, and all of it circulated as waste nitrogen because the kidneys did not excrete it, the figures shown in the table would be obtained.

TABLE I.

THEORETICAL AND ACTUAL VALUES OF NON-PROTEIN NITROGEN OF THE BLOOD RESULTING FROM NITROGEN RETENTION IN CERTAIN CASES OF NEPHRITIS.

	N of blood, mg. per 100 cc.			N grams retained during observation.
	At beginning of observation.	At end of observation.	Theoretical value at end of observation. *	
Case 1	30	37	152	92.0
" 2	30	38	116	65.0
" 3	25	34	93	51.0
" 4	30	37	165	101.4
" 5	29	27	119	69.1
" 6	71	74	117	35.3

* These figures represent the values obtained for non-protein nitrogen of the blood at the beginning of the observation plus the theoretical value due to retained nitrogen.

This table shows that a positive balance of nitrogen, in cases of nephritis on a mixed diet, is not necessarily followed by a corresponding increase in the non-protein nitrogen of the blood. Similar results have in the past been obtained in normal individuals.§ However, in clinical medicine, such a course of events is not given the recognition it deserves. It is evident that discretion must be exercised in interpreting a normal figure for non-protein nitrogen of the blood, as indicating that no nitrogen retention has taken place, and in considering a positive nitrogen balance as an absolute indication of the inability of the kidneys to excrete this substance.

3. On the Treatment of Hay Fever by Vaccination with Aqueous Extracts of Certain Plant Pollens.‖ G. H. A. CLOWES.

The purpose of this paper is to give a brief report of the results obtained in the course of the last four years on upward of one hundred hay-fever cases, treated by means of repeated injections of the extracts of certain plant pollens. The pollens employed were first dehydrated by means of a mixture of acetone and ether, and subsequently extracted with water—a method which is vastly superior to the freezing and thawing procedure of Dunbar, Noon and Freeman, owing to its greater simplicity and to the durability of the dry product. Although a large variety of pollens was tested, the majority of individuals were found to be sensitive to one of the two main groups: Graminaceæ, flowering for the most part in the spring, and Compositæ, flowering for the most part in the autumnal season. Cases were tested by means of the ophthalmic and cutaneous methods previously described,† a flush being produced in the eye of a sensitive individual by the introduction of a drop of a solution containing from one part in five hundred thousand to one part in a thousand of the pollen, based on original weight.

Although a limited number of individuals are sensitive to the pollen of both main groups, and exhibit hay-fever symptoms in both spring and autumn, a majority are sensitive only to the plants of a single group. Group reactions are frequently obtained, different individuals exhibiting varying degrees of sensitiveness to plants in the same group, but it is almost invariably the rule that sensitiveness to ragweed will be associated with sensitiveness to goldenrod and vice versa, although it is perfectly possible for individuals sensitive to ragweed and goldenrod to be entirely free from any sensitiveness to more distantly related members of the Compositæ family, dandelion for example, and vice versa.

A marked alleviation of symptoms and reduction in sensitiveness may be effected in the majority of cases by the injection of dilute extracts of the pollens to which the individual is sensitive, starting, preferably two or three weeks before the commencement of the season, with doses as small as 1 cc. of a one in five million to one in a million, increasing the dose at intervals of three or four days, until ten or twelve doses have been administered, the maximal dose employed being 1 cc. of a one in five thousand to 1 cc. of a one in a thousand. The results were controlled by comparison with untreated cases; and also by immunization of individuals sensitive to two widely divergent pollens against one only, thus proving the specificity of the immunity or desensitization produced.

Shortly after the conclusion of treatment sensitiveness once more develops, and within a period of from three to six months reaches a figure equal to that observed before treatment, but in those cases in which treatment has been extended over a period of three or four years, reduction in hay-fever symptoms is noted from year to year, which suggests the possibility that by continued treatment a cure may ultimately be effected. A certain number of cases exhibiting seasonal asthmatic symptoms, but without any of the other symptoms normally accompanying hay fever, have been considerably alleviated by pollen injections. From 25 to 30 per cent of the hay-fever cases thus far treated have experienced marked alleviation of symptoms. A further 30 or 40 per cent show a marked improvement, while the remainder are apparently entirely unaffected by the treatment. However, in view of the fact that cases of this latter type seldom exhibit any marked cutaneous or ophthalmic reaction, we are inclined to believe that we have not yet discovered the particular pollen varieties to which their symptoms are especially attributable. A non-specific immunization, or rather reduction in sensitiveness, may be effected in certain cases by administering large doses of calcium lactate. It is worthy of note that well-nourished individuals appear to respond most readily to treatment with calcium salts.

Sensitization attributable to other causes than pollens is occasionally confused with hay fever. We have, for example, observed

† Marshall and Davis: Jour. Biol. Chem., 1914, XVIII, 53.

§ Lüthje: Ztschr. f. klin. Med., 1902, XLIV, 22.

Lüthje u. Berger: Deutsch. Arch. f. klin. Med., 1904, LXXXI, 278.

Von Noorden u. Krug: Arch. f. Anat. u. Physiol., Physiol.-Abth., 1893, § 371.

‖ From the Biological-Chemical Department of the State Institute for the Study of Malignant Disease, Buffalo, New York.

† Clowes: A preliminary communication on certain specific reactions exhibited by hay-fever cases. Proc. Society for Experimental Biology and Medicine, 1913, X, pp. 69-72; also, A preliminary communication on the treatment of autumnal hay fever by vaccination with an aqueous extract of the pollen of ragweed. *Ibid.*

sensitization to a certain variety of flies, which was successfully treated by vaccination with a solution containing an extract of the flies in question. Marked cutaneous reactions have been obtained in the case of individuals sensitive to protein constituents of fish, horses, sheep's wool, apples, etc., from which it would appear that sensitization not only to pollens, but also to a large variety of foreign proteids, occurs more frequently than is generally appreciated, and is responsible, not only for hay fever and asthmatic symptoms, but probably also for certain gastro-intestinal and other disturbances of obscure origin.

The susceptibility to the development of sensitization phenomena appears to be, in a measure, an inherited characteristic. From data accumulated regarding certain families over a period of several generations, the occurrence of one or another form of sensitization occurs in such ratios as to suggest the advisability of further study in this direction. From the fact that cutaneous reactions are exhibited at any point in the body, and that a complement deviation reaction is frequently obtained in the blood, the sensitization in hay fever appears to be systemic, but all attempts to produce reactions in normal individuals, after incubating the pollen extract with the serum of a sensitive individual, have failed of result.

Attempts to produce immunity by means of a single dose of pollen extract do not appear to be very successful, from which we must conclude that hay fever differs essentially from ordinary protein sensitization.

DISCUSSION.

DR. FORD: I am sure you will all agree with me that the various phenomena connected with the problem of hay fever are in the main so complicated, particularly from the theoretical aspect of the subject, that it is extremely difficult to get a clear conception of it, and we are immensely indebted to Dr. Clowes for bringing out a number of points which are of exceptional value in its consideration. We take a great interest in hay fever in Baltimore, even though there may not be as much of the disease here as there is in the lake regions. There, hay fever is the great summer disease, and you will often see people in the street comparing notes as to the best place to go for relief. About the first of August there is an exodus of many of the able-bodied people in town.

It is interesting to note that most of the investigations were started by people who actually suffered from hay fever. For instance, Dunbar himself was a victim, and was thus stimulated to undertake the work. His investigations opened up an important field, not only in regard to this subject, but in regard to this whole chapter of immunity. I do not know definitely, but I believe the first pollen toxin was used in Baltimore. Dunbar came here about 1903, and brought some toxin and antitoxin with him. At that time a prominent man in Baltimore was suffering from an attack of hay fever. He suffered enough to require treatment, and some pollen antitoxin was administered to him. There were no results apparent, the symptoms did not ameliorate and the question naturally arose as to whether this individual was susceptible to the kind of pollen employed in making this particular antitoxin. To solve this problem a bit of the pollen toxin was dropped upon the victim's nasal mucosa. In consequence of this he developed a violent attack of hay fever with the characteristic symptoms.

This experiment demonstrated two important facts. One was that the antitoxin was not of any particular value. That was the conclusion forced upon Dunbar, and it has since been admitted that the treatment employed in Hamburg is not very satisfactory. The other point was that there are people in this country who are susceptible to the particular pollen Dunbar was using in Germany. His experiments are extremely interesting and painstaking. For instance, the question came up as to why it is that so many individuals suffer from hay fever at particular times of the year, individuals living in the city, who do not go into the country and do not come in contact with grasses giving off pollen to which they are susceptible. Dunbar invented a counting machine by which he estimated the amount of pollen in the atmosphere, and found that he could always obtain pollen granules in the air, even on the tops of high buildings. This brought out the practical impossibility of carrying out any effective measures to prevent the spread of pollen by elimination of particular weeds. In all districts, apparently, the pollen granules are so thickly spread in the atmosphere that individuals who are susceptible are certain to be attacked.

Investigations of this nature were especially stimulated by Ehrlich's side-chain theory, which about this time was at the height of its popularity. In that period of the development of immunology, if a man introduced a poison into an animal and obtained certain reactions, the serum of this animal afterward neutralizing the poison, it was usually admitted that we were dealing with a true toxin and antitoxin. I question if the conclusions reached by the immunologists of that period would be accepted so readily to-day as they were then. For instance, Dunbar found that animals treated with the pollen toxin produced a serum which deviated complement when brought in contact with the pollen. At the same time human beings, who were treated with the serum from the animals, showed apparently an amelioration of the hay-fever symptoms. This would hardly be accepted at the present time as the proof of true toxin and antitoxin action. Although Dunbar was at first quite convinced that horses, especially Arabian horses, produced true pollen antitoxin, this conclusion has apparently not been accepted by the majority of workers in this field. About 1902 Prof. Dunbar began a painstaking study of the vaccines against hay fever, and this work has opened up the whole subject of vaccination in this disease.

It is a difficult thing to explain the reactions which one sees in hay fever. The disease is comparatively simple clinically, as the symptoms are so characteristic that there is no doubt of the diagnosis. When we attempt to link up our theoretical knowledge of the disease with the symptoms, however, we are confronted by considerable obscurity. It is apparent that the patients show two sets of reactions at the same time. One of these we are inclined to ascribe to the condition of hypersensitiveness or anaphylaxis, whereas, the other is possibly to be explained as an immunity to the disease. It is quite evident from the work of Dr. Clowes and of others, that there are many interesting questions relating to hay fever yet to be solved.

Despite the criticism of Prof. Dunbar's work, it should be emphasized that the question as to whether he did or did not obtain a true pollen antitoxin is now of little moment. Dunbar deserves the greatest possible credit, because his work opened up the scientific study of hay fever itself, both from the clinical and the laboratory standpoint. If we compare what we have heard to-night concerning the etiology of this disease with what was taught in this school not so very many years ago, when hay fever was regarded as a neurosis, it is quite evident that science has made very definite progress in the last decade.

NOVEMBER 15, 1915.

As to the Cause of Aneurism of the Subclavian Artery in Cases of Cervical Rib. W. S. HALSTED and M. R. REID.

To appear in full in a later issue of the BULLETIN.

JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

NOVEMBER 8, 1915.

The meeting was called to order by the president, Dr. H. M. Thomas. The election of officers for the ensuing year was then held. Dr. Henry M. Hurd was elected president and Dr. Thomas R. Boggs, secretary.

Leonardo da Vinci's Anatomy. ARNOLD C. KLEBS.

To appear in full in a later issue of the BULLETIN.

NOTES ON NEW BOOKS.

A Text-Book of the Practice of Medicine. By HOBART AMORY HARE, B. Sc., M. D. Third edition, revised and enlarged. Price, $6. (*Philadelphia: Lea & Febiger, 1915.*)

This new and enlarged edition of Hare's Practice is presented in an attractive format, with excellent illustrations in black and white and colored plates of varying quality.

As heretofore, the greatest value of Dr. Hare's book lies in the personal side of his experience. Especially is this noteworthy in discussions of treatment. His opinions in this field are always interesting and should teach the student to consider the reason for any therapeutic measure before ordering it. T. R. B.

The Gold-Headed Cane. By WILLIAM MACMICHAEL, M. D. With an introduction by SIR WILLIAM OSLER, B. A., M. D., F. R. S.; and a preface by FRANCIS R. PACKARD, M. D. (*New York: Paul B. Hoeber, 1915.*)

The original work itself needs no encomium. Everyone who has written about the Gold-Headed Cane has taken his data from Macmichael's book, and the fact that two successive editions were published in 1827 and 1828, and that it was re-edited, with additions, in 1884, by Dr. William Munk, the historian of the Royal College of Physicians, is sufficient evidence of its popularity. In the present imprint, the style and spirit of the original are preserved in a beautiful and reverent manner, the illustrations and the original title page of John Murray's second edition are admirably reproduced, and the letter-press is worthy of Murray. Sir William Osler's introduction orients us as to the purpose of the present reprint, which he regards as a fitting memorial to Radcliffe, two hundred years after his death, the present war preventing the proper ceremonials in England. He gives admirable paragraphs on the present day status of the successive owners of the cane and regards the account of Mead as the best in the volume, that of Pitcairn as the poorest. Dr. Packard follows with a clear and informing account of Macmichael, and a history and bibliography of the different editions of his book. The new title-page, which precedes the facsimile, deserves a special note. It was designed by Frederick W. Goudy, that artist-craftsman who has surpassed all others of his guild in the number and variety of beautiful fonts of his own invention. Artistic designing of types is a new departure in America, where, until Goudy took it up, we had little approaching the work of Essex House, the Vale, Dove and Ashendeane Presses, or the Eragny and Morris imprints. A native of Bloomington, Ohio, once a bookkeeper in Chicago, Goudy made his first experiment in type designing in 1896, which was immediately honored by a check from the Dickenson Type Foundry of Boston. Losing his position in 1899, he took up this special field of decorative work, and for years labored at a starvation income, having to eke out his slender resources by designing placards and other advertisements for commercial firms. But his perseverance was rewarded in time, and, after founding the Village Press in 1903, he became known to all who are interested in beautiful printing which shall at the same time be grateful to the eyes of the reader. In this he was but following his master, Nicholas Jenson, the French engraver, who was among the first to do artistic printing in the fifteenth century, and whose masterpiece, the wonderful Venetian Eusebius of 1470, is even more soothing to read than the Oporinus types of the 1555 Vesalius, or the similar triumphs of Elzevier and Simon Colinæus. The reason is that the fonts are so cunningly conceived, the letters being founded flush with their bodies, that the curves and angles almost dovetail, yet afford an extraordinary amount of clean white space between them. Goudy has now to his credit more than thirty original fonts of these appealing letters, a record which, it is said, surpasses even the Golden Age of printing. As a gift-book of the keepsake kind, the Gold-Headed Cane is creditable to Dr. Packard's scholarship and Mr. Hoeber's enterprise, and, as Dr. Osler says, "is an indication of the zeal with which the study of the history of medicine has been taken up by the profession of the United States." F. H. G.

Muscle Spasm and Degeneration in Intrathoracic Inflammations and Light Touch Palpation. By F. M. POTTENGER, A. M., M. D., LL. D. Cloth, $2. (*St. Louis: C. V. Mosby Company, 1912.*)

A reading of this book undoubtedly makes one feel that he has in the past overlooked some interesting clinical phenomena. That muscle spasm occurs with intrathoracic inflammations is probable *a priori*, and at times is demonstrable. But the demonstration is either rare or difficult. It is to be expected that muscle spasm in the bony thoracic wall cannot be as easily detected as in the abdominal covering, and this is reason enough why we should attribute to the author, temporarily at least, a skill in technique not yet attainable by others. From our own imperfect investigations of the method, we cannot conclude that the diagnosis of intrathoracic conditions is aided thereby. But the author's observations are ingenious and will perhaps bear fruit. For his emphasis upon the serviceability of light percussion, the patients, more particularly, should be grateful. S. W.

La Tuberculose Inflammatoire. By A. PONCET, M. D., and R. LERICHE, M. D. Price, 7 francs. (*Paris: Octave Doin et fils, 1912.*)

According to the conception of the authors, "la tuberculose inflammatoire" is that form of tuberculosis in which the tuberculous noxus produces in the tissues merely a simple inflammatory reaction. In such a process the specific elements of the tuberculous reaction are lacking; there is no aggregation of mononuclear elements; there are no giant-cells. This non-specific reaction, the authors believe, may be elicited in any tissue, and appears under many clinical guises. The conception has already been rendered familiar to us by the work of Poncet on "tuberculous rheumatism," the atypical reaction being supposedly elicited by the tuberculous toxin and not by the tubercle bacillus itself. The argument for the wide-spread existence of such a form of tuberculosis rests upon the coincidence of unexplained inflammatory processes with definite tuberculous lesions elsewhere in the body, the two forms flaring up or quieting down together. To a certain degree the theory is attractive, but the dangerous fallacy attendant upon such argumentation arises from the great frequency of latent tuberculous lesions. It is easy to stretch the argument to the breaking-point by asserting that every human ill of hitherto unknown etiology must be an instance of "inflammatory tuberculosis" because the patient has in all probability a latent pulmonary tuberculosis or tuberculous adenitis! That the authors have succumbed to this insidious logic will be evident from a comparison of the copious index of these newly-found forms of tuberculosis with the scanty proof furnished to the eager reader. We cannot but be pleased with the wealth of interesting hypothesis; nevertheless, in most instances we remain constrained to skepticism. S. W.

Operative Surgery of the Nose, Throat and Ear. By HANAU W. LOEB, A. M., M. D. Vol. I. Cloth, $6. (*St. Louis: C. V. Mosby Company, 1914.*)

This publication is to appear in two volumes. The first deals with the surgical anatomy of the nose, throat, ear, neck and larynx, and also contains very instructive chapters on the direct examination of the bronchi and œsophagus. The second volume is to be voted to the more specialized surgery of the nasal cavities, throat and larynx.

The list of collaborators includes the names of the most distinguished American laryngologists. The plan of the book is to present the subject in concise, well-illustrated articles, written by men specially qualified for the assigned topics. The section by Dr. Mosher on the examination of the larynx, bronchi and œsophagus is particularly valuable. The chapter on the surgical anatomy of the nose contains many excellent drawings made from dissections. The last hundred pages are devoted to the plastic surgery of the nose and ear. All the most satisfactory plastic operations are given in detail, and, as a rule, the various steps are shown in illustrations.

This first volume contains three hundred and ninety pages: the print is large and clear. On the whole, it is a most excellent book and should be read by everyone interested in this special line of work. S. J. C.

Reducing Weight Comfortably. The Dietetic Treatment of Obesity. By Prof. Gustav Gaertner, M. D., Vienna. Cloth, $1.50. (*Philadelphia: J. B. Lippincott Company, 1914.*)

In this little book Professor Gaertner gives us in a most delightful manner the result of his long experience in the treatment of obesity. To quote his own words, he is "undertaking neither an historic presentation of the subject nor a criticism of other methods of treatment," but proposes to limit himself to a description of the methods by which he has "succeeded in reducing the weight of people living under the most different conditions."

The subject is treated in a conversational style, which makes the book a very readable and charming one. Prof. Gaertner has evidently applied common sense to his cures of obesity and has eliminated the use of the various preparations of the internal secretions, which in some of the monographs on the subject, at least, plays such an important rôle. He accomplishes his reduction cures purely by the limitation of diet, and, judging from the cases cited, he is very successful in doing so. The caloric value of the food is adjusted to the needs of each patient, and the results thus obtained are, without question, satisfactory. The weights of the diets are given in grams and Gaertner insists on the fact that every individual undergoing the treatment must weigh his food: "No scales, no cure," is his slogan.

It is a pity that in none of the cases is the caloric value of the food given. As a result of this omission, the tables lack some of the qualities that would make them of the greatest practical value. The treatment allows of any desired food, the quantity, however, being limited, while the amount of water to be taken is in no wise curtailed. These are only two of the many applications in which sound common sense has guided the author, and in regard to which there are many "fads and fancies," both among the laity and also among physicians.

Outside of the direct benefits from an obesity cure, which accrue to the individual from the point of view of vanity and greater physical well-being, Prof. Gaertner mentions certain conditions which are remarkably benefited by a reduction in weight. Thus in some of his patients he has noted a lowering of the blood pressure, the cure of certain forms of migraine, the relief of vomiting and heartburn, the disappearance of the flushes of the menopause and the correction of irregular menstruation.

Twelve Lectures on the Modern Treatment of Gonorrhœa in the Male. By P. Asch, M. D. Translated and Annotated by Faxton E. Gardner, M. D. 104 pages with illustrations. Cloth, $1. (*New York: Rebman Company, 1915.*)

In this book the author gives a concise résumé of the modern methods employed in the treatment of gonorrhœa by the German and French schools.

His treatment of acute gonorrhœa differs somewhat from the one usually employed in this country, inasmuch as he employs irrigations instead of injections in the early stages.

Asch uses electrargol, injected into the epididymis, for the treatment of acute epididymitis. In his hands this remedy has brought about very good results, and no impairment of function has ensued.

He prefers gonococcus vaccines to antigonococcic serum in the treatment of gonorrhœal arthritis and the various complications of gonorrhœa. His results, however, are not definitely given.

The last lecture is devoted almost entirely to urethroscopy, upon which he mainly depends for guidance in the diagnosis and treatment of chronic anterior urethritis. The pathology of the different lesions is taken up very briefly.

The annotations by the translator are valuable, in that they call attention to the various points in which the foreign methods differ from the American procedures in treating this disease.

Considered as a whole, the book is thoroughly up to date and deserves to be recommended. F. W. H.

Student's Text Book of Hygiene. By W. James Wilson, M. D., D. Sc., D. P. H. Price, $2.50. (*New York: The Rebman Company, 1915.*)

In a volume of a little more than 250 pages Dr. Wilson has presented the main facts and theories of hygiene as based upon his lectures on this subject at Queen's University, Belfast. Despite the author's evident leaning to the English school of hygienists, he sees more clearly than many of his co-workers the essential distinction between the science of hygiene and the various branches of it known as Preventive Medicine, Public Health and Sanitary Science. The great influence of von Pettenkofer is not, however, clearly recognized, although the work of Pasteur, Lister and Koch is properly evaluated. The book deals with principles rather than with laboratory methods and from this standpoint is well written, concise and yet readable. The chapters on Communicable Diseases and Tropical Diseases are especially good.

W. W. F.

A Manual of the Practice of Medicine. Prepared especially for students. By A. A. Stevens, A. M., M. D. Tenth edition. Price, $2.50. (*Philadelphia: W. B. Saunders Company, 1915.*)

The fact that ten editions have appeared since 1892 is evidence of the best that the book meets a demand. If students must use a compend, Stevens' Practice is the best of its kind.

The present edition shows that the author has kept it up to date.

The sections on general symptomatology at the beginning of each system—respiratory, digestive, etc.—are very good in bringing out the possible diagnostic relations of important symptoms.

Altogether, this edition will continue the hold of its predecessors on the student body. T. R. B.

The Practitioner's Encyclopædia of Medical Treatment. Edited by W. Langdon Brown, M. D., F. R. C. P., and J. Keogh Murphy, M. C., F. R. C. S., with an introduction by Sir Thomas Clifford Allbutt. Price, $8. (*London: Oxford University Press, 1915.*)

This book, which is a compilation of short articles by many physicians and surgeons of standing and experience, is an admirable one of its kind; it is comprehensive and fairly up to date in all the fields covered, and will form a valuable addition to the reference library of pharmacology and therapeutics.

Its large size is compensated for by the admirable lightness and clear type characteristic of the best English presses.

The first half is devoted to general and particular discussions of the methods of treatment for the diseases of the various systems. The second part takes up the agents used in treatment and contains a clear, concise and practical discussion of the different drugs and groups of drugs in the light of the most modern pharmacologic studies.

The index is excellent. T. R. B.

Diagnostic Methods. By RALPH W. WEBSTER, M. D., PH. D., Assistant Professor of Pharmacological Therapeutics and Instructor in Medicine in Rush Medical College, University of Chicago; Director of the Chicago Clinical Laboratory. Fourth edition. Price, $4.50 net. (*Philadelphia: P. Blakiston's Son & Co., 1914.*)

The fourth differs from the previous editions of this work chiefly in the addition of a consideration of many of the newer contributions to clinical diagnosis, such as methods for the estimation of the blood sugar, Lange's colloidal gold test for the cerebrospinal fluid, newer methods for staining spirochætæ in tissue, etc. The sections on the Wassermann reaction and the complement deviation tests in gonorrhœa have been elaborated. In addition a new and valuable chapter on clinical bacteriology has been added. Besides the above, many other tests, the clinical value of which have not yet been fully determined, the dialysation method of Abderhalden, the Herman-Perutz modification of the Porges test and others, have been outlined. The book is well indexed, clear and concise. It has all of the features which have recommended the previous editions to students and practitioners, as well as much valuable newer material. W. A. B.

Diseases of the Bronchi, Lungs and Pleura. By FREDERICK T. LORD, M. D. 590 pages. Cloth, $5. (*Philadelphia: Lea & Febiger, 1915.*)

This book is essentially a practical treatise on diseases of the respiratory organs, including the bronchi, pleura and lungs, exclusive of pulmonary tuberculosis. The author apparently realized that to include the last subject would be beyond the limits of this volume, but he has considered under various headings those conditions which might simulate pulmonary tuberculosis, and their differential diagnosis. His aim has been to formulate our present knowledge of these various diseases, as based upon a study of the literature and upon his own experience gleaned in the wards and pathological laboratories of the Massachusetts General Hospital. In dealing with various subjects included in his book a certain commendable individuality has been displayed. Though adhering in general to a well-systematized order of presentation, the author has held himself to no hard and fast rule, but has included special subject headings wherever the disease in question required it. This is perhaps best seen in his handling of lobar pneumonia. He has presented in a concise form the recent scientific advances and has included under each disease a commendable digest of those laboratory methods which may be of value in diagnosis or in treatment. Throughout the book foot-note references are given to the literature bearing upon any one subject, and so chosen as to make readily available the most important original articles. The book is well illustrated and well printed; it is singularly free from errors and makes very pleasant reading. The author has fully accomplished the aim which he had in mind, and has given us a book which will serve as an extremely valuable reference work on this subject. S. R. M.

Text-Book of Massage and Remedial Gymnastics. By L. L. DESPARD. Second Edition. Cloth, $4.50. (*London: Oxford University Press, 1914.*)

In this volume the technic of Mechanical Therapeutics has been set forth in a manner which makes it somewhat difficult for the student to grasp the fundamental principles underlying these relatively simple procedures. The voluminous and unnecessary details give the reader a confusing idea of the subject and the book, therefore, to a certain extent, fails in the purpose for which it was written.

The question of "indication and contra-indication" has been treated in a "cure-all" spirit. In this respect the writer shows an unfortunate tendency very common among writers on this subject; unfortunate, because it is largely responsible for the prevalent antagonism of the medical profession toward a treatment which is of inestimable value when used in the right place and at the right time. C. R. A.

A Text-Book for Midwives. By JOHN S. FAIRBAIRN. Cloth, $3.75. (*Oxford Medical Publication, 1914.*)

This addition "to the many text-books" for midwives is couched in a style which might justly awake unfavorable criticism. The subject matter is simple and for the most part well chosen; but the diction is not in accord with this commendable simplicity. There is a tendency toward the use of purely technical terms that would be staggering to the average midwife—overwhelming to the class as we know it in this country. If the English people have midwives who can read this book intelligently, they are to be congratulated. The illustrations are generally very good, but the author's choice has not been exceptionally so; many of them might have been excluded with profit and others might equally profitably have been inserted. The sequence of the subject matter leaves little to be desired and the introductory chapters on anatomy, physiology and bacteriology are excellent. The concluding chapters on venereal infection and uterine cancer are steps in the direction of public education, which should be well received.

From the standpoint of obstetrical teaching, one is rather surprised to notice the prominence given to the details of vaginal douching. At a time when the consensus of opinion is certainly against vaginal douching, *intra-partum* or *ante-partum* or *post-partum*, it would seem that the midwife should be impressed with the reasons for its avoidance rather than with numerous indications for its use. The continued reference to the many uses found for antiseptic solutions shows that the writer has not yet accurately estimated the efficiency of these drugs when used in the form of a momentary application. The occasional inaccuracies in the subject matter are presumably due to a desire not to complicate the subjects under discussion by citing well known exceptions.

E. D. PLASS.

Cancer: Its Causes and Treatment. By L. DUNCAN BULKLEY, M. D. Cloth, $1.50. (*New York: Paul B. Hoeber, 1915.*)

The six lectures contained in this book show how the idea of the constitutional cause of cancer continues to exert its influence even at the present time. The author, while conceding the influence of various contributing causes in the development of the local lesion, is convinced that cancer is primarily a constitutional disease, the result of imperfect metabolism which he attributes especially to the excessive consumption of meat, tea, coffee and alcohol. So long as the true nature of cancer is unknown, every unbiased, intelligent effort to discover its cause should possess some value, but modern research and clinical observation tend to show more and more clearly that the disease is primarily a local one, and the old theory of its constitutional or humoral cause is no longer seriously considered. No new arguments in its support are offered in this work. The author, while recognizing the advances of surgery in the treatment of cancer, and also that the hope of a surgical cure depends upon early operative interference, nevertheless advocates a course of hygienic and dietetic treatment, in early as well as advanced cancer, before resorting to operation. The deplorable effect of such teaching is obvious. Its tendency to discourage operative interference, on account of the apparent hopelessness of removing what is merely the local manifestation of a general disease, and on the other hand to foster a dependence upon general remedies to cure the local lesion, until the opportunity for a radical cure is passed, is especially regrettable, in view of the educational campaign which is being carried on to enlighten the public regarding the natural history of cancer and the possibility of its operative relief. E. H.

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